EP04/9108

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Signed Stephen Hordley.

Dated 15 July 2003

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13SEP02 E747846_2 D00019
P01/7700 0.00-0221143.1

Request for grant of a patent

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The Patent Office
Cardiff Road
Newport
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12 SEP 2002

1. Your reference

P031753GB

2. Patent application number
(The Patent Office will fill in this part)

0221143.1

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Bayer AG
D-51368 Leverkusen
Germany

Patents ADP number *(if you know it)*

8100414001

If the applicant is a corporate body, give the country/state of its incorporation

Germany

4. Title of the invention

Dihydropyridinone derivatives

5. Name of your agent *(if you have one)*

Carpmaels & Ransford

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

43 Bloomsbury Square
London
WC1A 2RA

Patents ADP number *(if you know it)*

83001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
GB	0219894.3	27/08/2002

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body

See note (d))

Yes

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9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	65
Claim(s)	10
Abstract	1
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature: Carpmaels & Ransford — Date: 12th September 2002

Carpmaels & Ransford

12. Name and daytime telephone number of person to contact in the United Kingdom: **Adrian J. FISHER** — **020-7242 8692**

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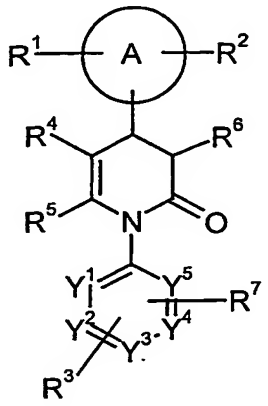
Dihydropyridinone derivatives

The present invention relates to novel dihydropyridinone derivatives, processes for their preparation, and their use in medicaments, especially for the treatment of chronic obstructive pulmonary diseases.

The fibrous protein elastin, which comprises an appreciable percentage of all protein content in some tissues, such as the arteries, some ligaments and the lungs, can be hydrolysed or otherwise destroyed by a select group of enzymes classified as elastases. Human leukocyte elastase (HLE, EC 3.4.21.37), also known as human neutrophil elastase (HNE), is a glycosylated, strongly basic serine protease and is found in the azurophilic granules of human polymorphonuclear leukocytes (PMN). HNE is released from activated PMN and has been implicated causally in the pathogenesis of acute and chronic inflammatory diseases. HNE is capable of degrading a wide range of matrix proteins including elastin, and in addition to these actions on connective tissue HNE has a broad range of inflammatory actions including upregulation of IL-8 gene expression, oedema formation, mucus gland hyperplasia and mucus hypersecretion. Pulmonary diseases where HNE is believed to play a role include lung fibrosis, pneumonia, acute respiratory distress syndrome (ARDS), pulmonary emphysema, including smoking-induced emphysema, chronic obstructive pulmonary diseases (COPD) and cystic fibrosis. HNE has also been causally implicated in rheumatoid arthritis, atherosclerosis, brain trauma, cancer and related conditions in which neutrophil participation is involved. Thus, inhibitors of HLE activity can be potentially useful in the treatment of a number of inflammatory diseases, especially of chronic obstructive pulmonary diseases [R.A. Stockley, *Neutrophils and protease/antiprotease imbalance*, Am. J. Respir. Crit. Care 160, S49-S52 (1999)].

Ethyl 6-amino-1,4-bis(4-chlorophenyl)-5-cyano-2-methyl-1,4-dihydro-3-pyridinecarboxylate has been synthesized and tested for potential antimicrobial activity as described in A.W. Erian et al., *Pharmazie* 53 (11), 748-751 (1998).

The present invention relates to compounds of the general formula (I)



(I),

wherein

A represents an aryl or heteroaryl ring,

R^1, R^2 and R^3 independently from each other represent hydrogen, halogen, nitro, cyano, trifluoromethyl, C_1-C_6-alkyl, hydroxy, C_1-C_6-alkoxy or trifluoromethoxy, wherein C_1-C_6-alkyl and C_1-C_6-alkoxy can be further substituted with one to three identical or different radicals selected from the group consisting of hydroxy and C_1-C_4-alkoxy,

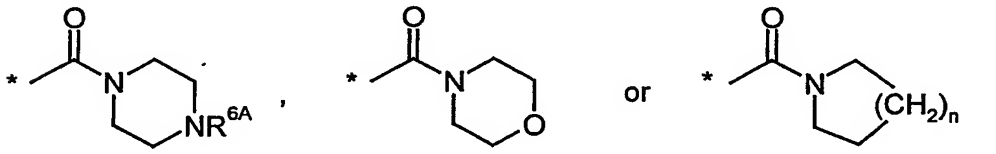
R^4 represents C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, hydroxycarbonyl, aminocarbonyl, mono- or di-C_1-C_4-alkylaminocarbonyl or cyano, wherein C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, mono- and di-C_1-C_4-alkylaminocarbonyl can be substituted with one to three identical or different radicals selected from the group consisting of hydroxy, C_1-C_4-alkoxy, hydroxycarbonyl, C_1-C_4-alkoxycarbonyl, amino, mono- and di-C_1-C_4-alkylamino, aminocarbonyl, mono- and di-C_1-C_4-alkylaminocarbonyl, C_1-C_4-alkylcarbonylamino and heteroaryl,

R^5 represents C_1-C_4-alkyl,

R^6 represents hydrogen, cyano, aminocarbonyl, mono- or di-C_1-C_4-alkylaminocarbonyl, C_3-C_8-cycloalkylaminocarbonyl, C_1-C_6-alkylcarbonyl, hydroxycarbonyl or C_1-C_6-alkoxycarbonyl, wherein mono- and di-C_1-C_4-alkylaminocarbonyl, C_1-C_6-alkylcarbonyl and C_1-C_6-alkoxycarbonyl can be substituted with one to three identical or different radicals selected from the group consisting of hydroxy, C_1-C_4-alkoxy, hydroxycarbonyl, C_1-C_4-alkoxycarbonyl, amino, mono- and di-C_1-C_4-alkylamino, aminocarbonyl, mono- and di-C_1-C_4-alkylaminocarbonyl, C_1-C_4-alkylcarbonylamino, phenyl and heteroaryl,

or

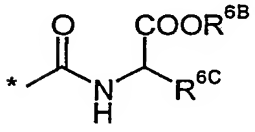
R^6 represents a moiety of the formula



wherein R^{6A} is selected from the group consisting of hydrogen and C_1-C_6-alkyl, and n represents an integer of 1 or 2,

or

R^6 represents a moiety of the formula



wherein R^{6B} is selected from the group consisting of hydrogen and C_1-C_6-alkyl, and R^{6C} is an amino acid side chain,

R^7 represents hydrogen, halogen, nitro, cyano, trifluoromethyl, C_1-C_6-alkyl, hydroxy, C_1-C_6-alkoxy or trifluoromethoxy, wherein C_1-C_6-alkyl and C_1-C_6-alkoxy can be further substituted with one to three identical or different radicals selected from the group consisting of hydroxy and C_1-C_4-alkoxy,

and

Y^1, Y^2, Y^3, Y^4 and Y^5 independently from each other represent CH or N, wherein the ring contains either 0, 1 or 2 nitrogen atoms.

The compounds according to this invention can also be present in the form of their salts, hydrates and/or solvates.

Physiologically acceptable salts are preferred in the context of the present invention.

Physiologically acceptable salts according to the invention are non-toxic salts which in general are accessible by reaction of the compounds (I) with an inorganic or organic base or acid conventionally used for this purpose. Non-limiting examples of pharmaceutically acceptable salts of compounds (I) include the alkali metal salts, e.g. lithium, potassium and sodium salts, the alkaline earth metal salts such as magnesium and calcium salts, the quaternary ammonium salts such as, for example, triethyl ammonium salts, acetates, benzene sulphonates, benzoates, dicarbonates, disulphates, ditartrates, borates, bromides, carbonates, chlorides, citrates, dihydrochlorides, fumarates, gluconates, glutamates, hexyl resorcinates, hydrobromides, hydrochlorides, hydroxynaphthoates, iodides, isothionates, lactates, laurates, malates, maleates, mandelates, mesylates, methylbromides, methylnitrates, methylsulphates, nitrates, oleates, oxalates, palmitates, pantothenates, phosphates, diphosphates,

polygalacturonates, salicylates, stearates, sulphates, succinates, tartrates, tosylates, valerates, and other salts used for medicinal purposes.

Hydrates of the compounds of the invention or their salts are stoichiometric compositions of the compounds with water, such as for example hemi-, mono-, or dihydrates.

Solvates of the compounds of the invention or their salts are stoichiometric compositions of the compounds with solvents.

The present invention includes both the individual enantiomers or diastereomers and the corresponding racemates or diastereomeric mixtures of the compounds according to the invention and their respective salts. In addition, all possible tautomeric forms of the compounds described above are included according to the present invention. The diastereomeric mixtures can be separated into the individual isomers by chromatographic processes. The racemates can be resolved into the respective enantiomers either by chromatographic processes on chiral phases or by resolution.

In the context of the present invention, the substituents, if not stated otherwise, in general have the following meaning:

Alkyl in general represents a straight-chain or branched hydrocarbon radical having 1 to 6, preferably 1 to 4 carbon atoms. Non-limiting examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, hexyl, isohexyl. The same applies to radicals such as alkoxy, alkylamino, alkoxycarbonyl and alkoxycarbonylamino.

Alkoxy illustratively and preferably represents methoxy, ethoxy, n-propoxy, isopropoxy, tert.-butoxy, n-pentoxy and n-hexoxy.

Alkylcarbonyl in general represents a straight-chain or branched hydrocarbon radical having 1 to 6, preferably 1 to 4 carbon atoms which has a carbonyl function at the position of attachment. Non-limiting examples include formyl, acetyl, n-propionyl, n-butyryl, isobutyryl, pivaloyl, n-hexanoyl.

Alkoxycarbonyl illustratively and preferably represents methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert.-butoxycarbonyl, n-pentoxycarbonyl and n-hexoxycarbonyl.

Alkylamino represents an alkylamino radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylamino, ethylamino, n-propylamino, isopropylamino, tert.-butylamino, n-pentylamino, n-hexylamino, *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-n-propylamino, *N*-isopropyl-*N*-n-propylamino, *N*-tert.-butyl-*N*-methylamino, *N*-ethyl-*N*-n-pentylamino and *N*-n-hexyl-*N*-methylamino.

Alkylaminocarbonyl represents an alkylaminocarbonyl radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, n-hexylaminocarbonyl, *N,N*-dimethylaminocarbonyl, *N,N*-diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-methyl-*N*-n-propylaminocarbonyl, *N*-isopropyl-*N*-n-propylaminocarbonyl, *N*-tert.-butyl-*N*-methylaminocarbonyl, *N*-ethyl-*N*-n-pentylamino-carbonyl and *N*-n-hexyl-*N*-methylaminocarbonyl.

Cycloalkylaminocarbonyl represents a cycloalkylaminocarbonyl radical having one or two (independently selected) cycloalkyl substituents with 3 to 8, preferably 4 to 6 ring carbon atoms which is bound via a carbonyl group, illustratively and preferably representing cyclopropylaminocarbonyl, cyclobutylaminocarbonyl, cyclopentylaminocarbonyl, cyclohexylaminocarbonyl and cycloheptylaminocarbonyl.

Aryl represents a mono- to tricyclic aromatic carbocyclic radical having generally 6 to 14 carbon atoms, illustratively and preferably representing phenyl, naphthyl and phenanthrenyl.

Heteroaryl represents an aromatic mono- or bicyclic radical having generally 5 to 10 and preferably 5 or 6 ring atoms and up to 5 and preferably up to 4 hetero atoms selected from the group consisting of S, O and N, illustratively and preferably representing thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyridyl, pyrimidyl, pyridazinyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl.

Halogen represents fluorine, chlorine, bromine and iodine.

Amino acid side chain represents the organic substituent of an α-amino acid, which is bound to the α-carbon atom of the amino acid. Preferred are the side chains of natural α-amino acids.

These are for example hydrogen (glycine), methyl (alanine), propan-2-yl (valine), 2-methyl-propan-1-yl (leucine), 1-methyl-propan-1-yl (isoleucine), (3-indolyl)-methyl (tryptophan), benzyl (phenylalanine), methylthioethyl (methionine), hydroxymethyl (serine), p-hydroxybenzyl (tyrosine), 1-hydroxy-ethan-1-yl (threonine), mercaptomethyl (cysteine), carbamoylmethyl (asparagine), carbamoylethyl (glutamine), carboxymethyl (aspartic acid), carboxyethyl (glutamic acid), 4-aminobutan-1-yl (lysine), 3-guanidinopropan-1-yl (arginine), imidazol-4-ylmethyl (histidine), 3-ureidopropan-1-yl (citrulline), mercaptoethyl (homocysteine), hydroxyethyl (homoserine), 4-amino-3-hydroxybutan-1-yl (hydroxylysine), 3-amino-propan-1-yl (ornithine).

When stated, that Y^1, Y^2, Y^3, Y^4 and Y^5 represent CH or N, CH shall also stand for a ring carbon atom, which is substituted with a substituent R^3 or R^7.

A * symbol next to a bond denotes the point of attachment in the molecule.

In another embodiment, the present invention relates to compounds of general formula (I), wherein

A represents an aryl ring,

R^1, R^2 and R^3 independently from each other represent hydrogen, fluoro, chloro, bromo, nitro, cyano, methyl, ethyl, trifluoromethyl or trifluoromethoxy,

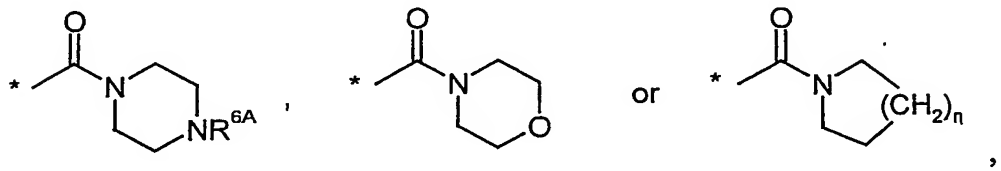
R^4 represents C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl or cyano, wherein C_1-C_6-alkylcarbonyl and C_1-C_6-alkoxycarbonyl can be substituted with one to two identical or different radicals selected from the group consisting of hydroxy, methoxy, hydroxycarbonyl, methoxycarbonyl, amino, mono- and di-C_1-C_4-alkylamino,

R^5 represents methyl or ethyl,

R^6 represents hydrogen, cyano, aminocarbonyl, mono- or di-C_1-C_4-alkylamino-carbonyl, hydroxycarbonyl or C_1-C_6-alkoxycarbonyl,

or

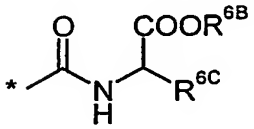
R^6 represents a moiety of the formula



wherein R^{6A} is selected from the group consisting of hydrogen, methyl and ethyl, and n represents an integer of 1 or 2,

or

R^6 represents a moiety of the formula



,

wherein R^{6B} is selected from the group consisting of hydrogen, methyl and ethyl, and R^{6C} is an amino acid side chain,

R^7 represents hydrogen, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, methyl or ethyl,

and

Y^1, Y^2, Y^3, Y^4 and Y^5 each represent CH.

In another embodiment, the present invention relates to compounds of general formula (I), wherein

A represents a phenyl ring,

R^1 represents hydrogen or methyl,

R^2 represents cyano, bromo or nitro,

R^3 represents hydrogen,

R^4 represents C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxycarbonyl or cyano, wherein C_1-C_4-alkylcarbonyl and C_1-C_4-alkoxycarbonyl can be substituted with hydroxycarbonyl or C_1-C_4-alkoxycarbonyl,

R^5 represents methyl,

R^6 represents hydrogen, cyano, aminocarbonyl, mono- or di-C_1-C_4-alkylaminocarbonyl, hydroxycarbonyl or C_1-C_6-alkoxycarbonyl,

R^7 represents trifluoromethyl or nitro,

and

Y^1, Y^2, Y^3, Y^4 and Y^5 each represent CH.

In another embodiment, the present invention relates to compounds according to general formula (I), wherein A is phenyl.

In another embodiment, the present invention relates to compounds according to general formula (I), wherein R^1 is hydrogen.

In another embodiment, the present invention relates to compounds according to general formula (I), wherein R^2 is cyano, especially wherein A is phenyl and R^2 is cyano located in para-position relative to the dihydropyridinone ring.

In another embodiment, the present invention relates to compounds according to general formula (I), wherein R^3 is hydrogen.

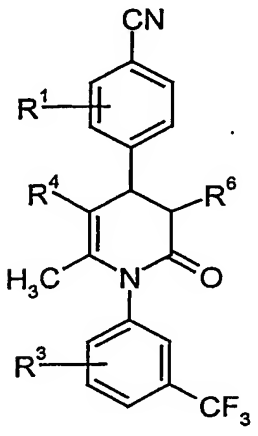
In another embodiment, the present invention relates to compounds according to general formula (I), wherein R^4 is C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl or cyano.

In another embodiment, the present invention relates to compounds according to general formula (I), wherein R^5 is methyl.

In another embodiment, the present invention relates to compounds according to general formula (I), wherein R^6 is hydrogen, cyano, aminocarbonyl, mono- and di-methyl- or -ethylaminocarbonyl, methoxycarbonyl or ethoxycarbonyl.

In another embodiment, the present invention relates to compounds according to general formula (I), wherein R^7 is trifluoromethyl or nitro.

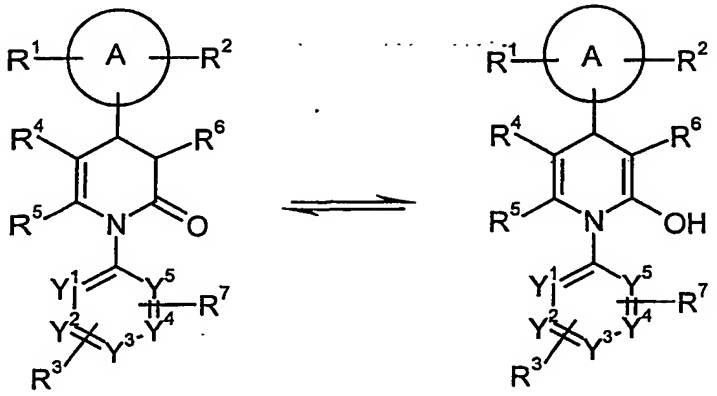
In another embodiment, the present invention relates to compounds of general formula (IA)



(IA),

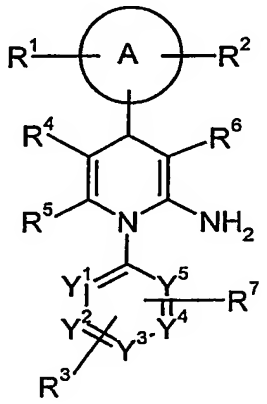
wherein R^1, R^3, R^4 and R^6 have the meaning indicated above.

The compounds of the present invention can enolize into the corresponding enoles:



In another embodiment, the present invention relates to processes for synthesizing the compounds of general formula (I), characterized in that

[A] compounds of the general formula (II)



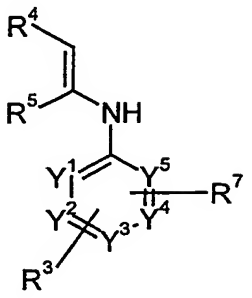
(II),

wherein R^1 to R^7, A and Y^1 to Y^5 have the meaning described above,

are hydrolyzed with water,

or

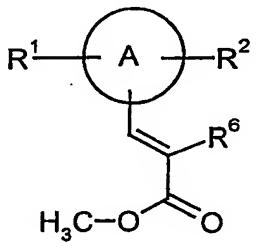
[B] compounds of the general formula (III)



(III),

wherein R^3, R^4, R^5, R^7, and Y^1 to Y^5 have the meaning described above,

are reacted with compounds of the general formula (IX)

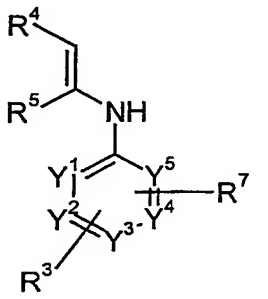


(IX),

wherein R^1, R^2, R^6 and A have the meaning described above,

or

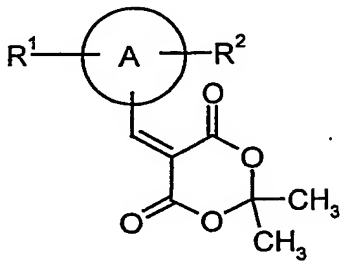
[C] compounds of the general formula (III)



(III),

wherein R^3, R^4, R^5, R^7, and Y^1 to Y^5 have the meaning described above,

are reacted with compounds of the general formula (VIII)



(VIII),

wherein R^1 and R^2 have the meaning described above.

Process [A]

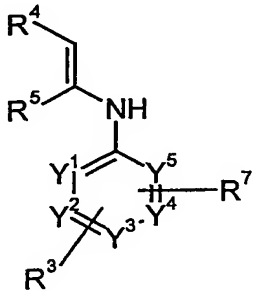
Suitable solvents for the process are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, diisopropyl ether, 1,2-dimethoxyethane, dioxan or tetrahydrofuran, ethylacetate, acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, or alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or t-butanol, or hydrocarbons such as pentane, hexane, cyclohexane, benzene, toluene or xylene, or halogeno-hydrocarbons such as dichloromethane, dichloroethane, trichloromethane or chlorobenzene. It is also possible to use mixtures of the above-mentioned solvents. Preferred for the process is water and acetic acid.

The process can take place in the presence of an acid. Suitable acids for the process are generally inorganic or organic acids. These preferably include carboxylic acids, such as, for example acetic acid or trifluoroacetic acid, or sulfonic acids, such as, for example, methanesulfonic acid or p-toluenesulfonic acid. Preference is given to acetic acid or trifluoroacetic acid. The acid is employed in an amount from 0.25 mol to 100 mol, relative to 1 mol of the compound of the general formula (II).

The process is in general carried out in a temperature range from +20°C to +150°C, preferably from +60°C to +130°C.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

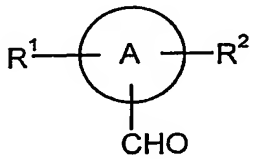
The compounds of general formula (II) can be synthesized by condensing compounds of general formula (III)



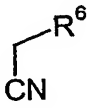
(III),

wherein R^3, R^4, R^5, R^7, and Y^1 to Y^5 have the meaning described above,

in the presence of a base, in a three-component-reaction, with compounds of the general formulas (IV) and (V)



(IV)



(V),

wherein R^1, R^2, R^6 and A have the meaning described above. Alternatively, in a first step compounds of the general formulas (IV) and (V) can be reacted, and the resulting product is reacted with or without isolation with compounds of the general formula (III) in a second step.

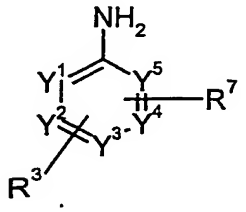
Suitable solvents for the process are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, diisopropyl ether, 1,2-dimethoxyethane, dioxan or tetrahydrofuran, ethylacetate, acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, or alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or t-butanol, or hydrocarbons such as pentane, hexane, cyclohexane, benzene, toluene or xylene, or halogeno-hydrocarbons such as dichloromethane, dichloroethane, trichloromethane or chlorobenzene. It is also possible to use mixtures of the above-mentioned solvents. Preferred for the process is ethanol.

Suitable bases for the process are generally inorganic or organic bases. These preferably include cyclic amines, such as, for example, piperidine, morpholine, N-methylmorpholine, pyridine or 4-N,N-dimethylaminopyridine, or (C_1-C_4)-trialkyl-amines, such as, for example, triethylamine or diisopropylethylamine. Preference is given to piperidine. The base is employed in an amount from 0.1 mol to 10 mol, preferably from 0.1 mol to 1 mol, relative to 1 mol of the compound of the general formula (II).

The process is in general carried out in a temperature range from +20°C to +150°C, preferably from +60°C to +130°C.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

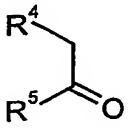
The compounds of general formula (III) can be synthesized by reacting compounds of general formula (VI)



(VI),

wherein R^3, R^7, and Y^1 to Y^5 have the meaning described above,

with compounds of the general formula (VII)



(VII),

wherein R^4 and R^5 have the meaning described above.

Suitable solvents for the process are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, diisopropyl ether, 1,2-dimethoxyethane, dioxan or tetrahydrofuran, ethylacetate, acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, or alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or t-butanol, or hydrocarbons such as pentane, hexane, cyclohexane, benzene, toluene or xylene, or halogeno-hydrocarbons such as dichloromethane, dichloroethane, trichloromethane or chlorobenzene. For the process also acetic acid can be employed as solvent. It is also possible to use mixtures of the above-mentioned solvents. Preferred for the process is ethanol, toluene or benzene.

Suitable acids for the process are generally inorganic or organic acids. These preferably include carboxylic acids, such as, for example acetic acid or trifluoroacetic acid, or sulfonic acids, such as, for example, methanesulfonic acid or p-toluenesulfonic acid. Preference is given to acetic acid or trifluoroacetic acid. The acid is employed in an

amount from 0.25 mol to 100 mol, relative to 1 mol of the compounds of the general formulas (V) and (VI), respectively.

The process is in general carried out in a temperature range from +20°C to +150°C, preferably from +60°C to +130°C.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The compounds of the general formulas (IV), (V), (VI) and (VII) are known per se, or they can be prepared by customary methods.

Process [B]

For process [B], compounds of the general formula (IX) can be prepared in situ or in a first step compounds of the general formulas (IV) and (X) can be reacted, and the resulting product is reacted with compounds of the general formulas (III) in a second step.

Suitable solvents for the process are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, diisopropyl ether, 1,2-dimethoxyethane, dioxan or tetrahydrofuran, ethylacetate, acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, or alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or t-butanol, or hydrocarbons such as pentane, hexane, cyclohexane, benzene, toluene or xylene, or halogeno-hydrocarbons such as dichloromethane, dichloroethane, trichloromethane or chlorobenzene. It is also possible to use mixtures of the above-mentioned solvents. Preferred for the process is ethanol.

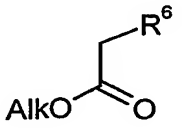
Suitable bases for the process are generally inorganic or organic bases. These preferably include cyclic amines, such as, for example, piperidine, morpholine, N-methyl-

morpholine, pyridine or 4-N,N-dimethylaminopyridine, or (C_1-C_4)-trialkyl-amines, such as, for example, triethylamine or diisopropylethylamine. Preference is given to piperidine. The base is employed in an amount from 0.1 mol to 10 mol, preferably from 0.1 mol to 1 mol, relative to 1 mol of the compound of the general formula (II).

The process is in general carried out in a temperature range from +20°C to +150°C, preferably from +60°C to +130°C.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The compounds of the general formula (IX) are known per se, or they can be prepared by reacting compounds of general formula (IV), wherein R^1, R^2 and A have the meaning described above, with compounds of general formula (X)



(X),

wherein R^6 has the meaning described above and Alk stands for alkyl, in the presence of a base.

Suitable solvents for the process are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, diisopropyl ether, 1,2-dimethoxyethane, dioxan or tetrahydrofuran, ethylacetate, acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, or alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or t-butanol, or hydrocarbons such as pentane, hexane, cyclohexane, benzene, toluene or xylene, or halogeno-hydrocarbons such as dichloromethane, dichloroethane, trichloromethane or chlorobenzene. It is also

possible to use mixtures of the above-mentioned solvents. Preferred for the process is methanol, ethanol or toluene.

Suitable bases for the process are generally inorganic or organic bases. These preferably include cyclic amines, such as, for example, piperidine, morpholine, N-methylmorpholine, pyridine or 4-N,N-dimethylaminopyridine, or (C_1-C_4)-trialkyl-amines, such as, for example, triethylamine or diisopropylethylamine. Preference is given to piperidine. The base is employed in an amount from 0.1 mol to 10 mol, preferably from 1 mol to 3 mol, relative to 1 mol of the compound of the general formula (X).

The process is in general carried out in a temperature range from +20°C to +150°C, preferably from +60°C to +130°C.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The compounds of the general formula (X) are known per se, or they can be prepared by customary methods.

Process [C]

Suitable solvents for the process are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, diisopropyl ether, 1,2-dimethoxyethane, 1-methoxy-2-(2-methoxyethoxy)-ethane, dioxan or tetrahydrofuran, ethylacetate, acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, or alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or t-butanol, or hydrocarbons such as pentane, hexane, cyclohexane, benzene, toluene or xylene, or halogeno-hydrocarbons such as dichloromethane, dichloroethane, trichloromethane or chlorobenzene. It is also possible to use mixtures of the above-mentioned solvents. Preferred for the process is 1-methoxy-2-(2-methoxyethoxy)-ethane or acetic acid.

The process is in general carried out in a temperature range from +20°C to +200°C, preferably from +100°C to +180°C.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The compounds of the general formula (VIII) can be synthesized by reacting compounds of general formula (IV), wherein R^1 and R^2 have the meaning described above, with 2,2-dimethyl-1,3-dioxane-4,6-dione.

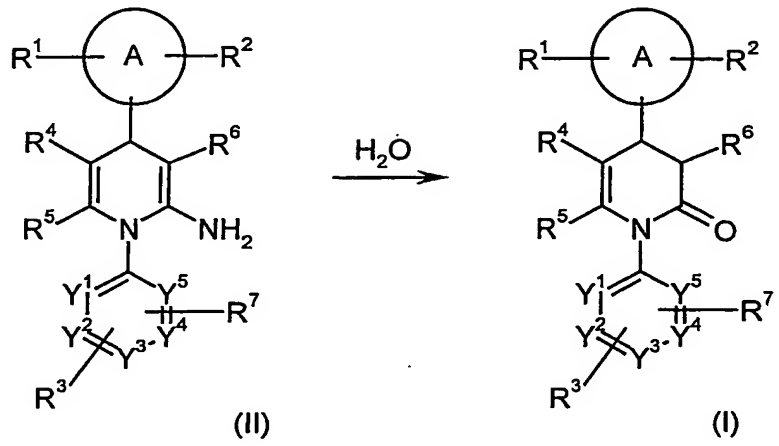
Suitable solvents for the process are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, diisopropyl ether, 1,2-dimethoxyethane, dioxan or tetrahydrofuran, ethylacetate, acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, or alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or t-butanol, or hydrocarbons such as pentane, hexane, cyclohexane, benzene, toluene or xylene, or halogeno-hydrocarbons such as dichloromethane, dichloroethane, trichloromethane or chlorobenzene. It is also possible to use mixtures of the above-mentioned solvents. Preferred for the process is water.

The process is in general carried out in a temperature range from +20°C to +150°C, preferably from +60°C to +130°C.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

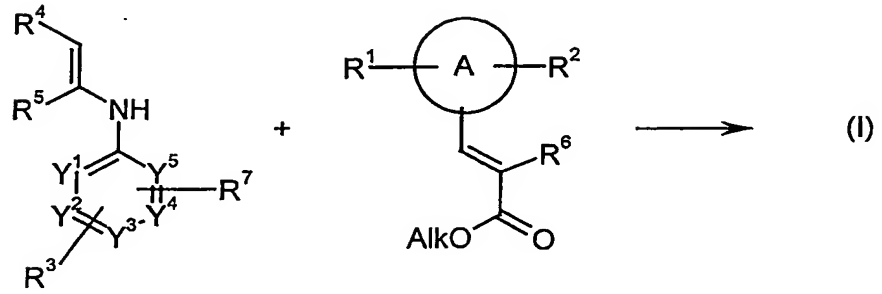
The above-mentioned methods can be illustrated by the following schemes:

[A]



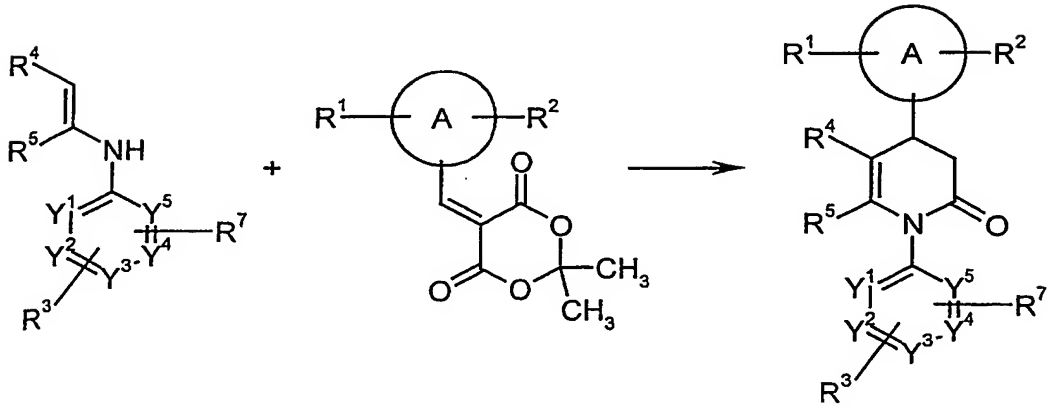
(II) (I)

[B]



(I)

[C]



The compounds according to the invention exhibit an unforeseeable, useful pharmacological and pharmacokinetic activity spectrum.

They are therefore suitable for use as medicaments for the treatment and/or prophylaxis of disorders in humans and animals.

Surprisingly, the compounds of the present invention show human neutrophil elastase (HNE) inhibitory activity and are therefore suitable for the preparation of medicaments for the treatment of diseases associated with HNE activity. They may thus provide an effective treatment of acute and chronic inflammatory processes, such as rheumatoid arthritis, atherosclerosis, and especially of acute and chronic pulmonary diseases, such as lung fibrosis, cystic fibrosis, pneumonia, acute respiratory distress syndrome (ARDS), in particular pulmonary emphysema, including smoking-induced emphysema, and chronic obstructive pulmonary diseases (COPD). They may also provide an effective treatment of brain trauma, cancer and other conditions in which neutrophil participation is involved.

The present invention further provides medicaments containing at least one compound according to the invention, preferably together with one or more pharmacologically safe excipient or carrier substances, and also their use for the above-mentioned purposes.

The active component can act systemically and/or locally. For this purpose, it can be applied in a suitable manner, for example orally, parenterally, pulmonally, nasally, sublingually, lingually, buccally, rectally, transdermally, conjunctivally, otically or as an implant.

For these application routes, the active component can be administered in suitable application forms.

Useful oral application forms include application forms which release the active component rapidly and/or in modified form, such as for example tablets (non-coated and coated tablets, for example with an enteric coating), capsules, sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, solutions and aerosols.

Parenteral application can be carried out with avoidance of an absorption step (intravenously, intraarterially, intracardially, intraspinally or intralumbarly) or with inclusion of an absorption (intramuscularly, subcutaneously, intracutaneously, percutaneously or intraperitoneally). Useful parenteral application forms include injection and infusion preparations in the form of solutions, suspensions, emulsions, lyophilisates and sterile powders.

Forms suitable for other application routes include for example inhalatory pharmaceutical forms (including powder inhalers, nebulizers), nasal drops/solutions, sprays; tablets or capsules to be administered lingually, sublingually or buccally, suppositories, ear and eye preparations, vaginal capsules, aqueous suspensions (lotions, shake mixtures), lipophilic suspensions, ointments, creams, milk, pastes, dusting powders or implants.

The active components can be converted into the recited application forms in a manner known per se. This is carried out using inert non-toxic, pharmaceutically suitable excipients. These include inter alia carriers (for example microcrystalline cellulose), solvents (for example liquid polyethylene glycols), emulsifiers (for example sodium dodecyl sulphate), dispersing agents (for example polyvinyl-pyrrolidone), synthetic and natural biopolymers (for example albumin), stabilizers (for example antioxidants such as ascorbic acid), colorants (for example inorganic pigments such as iron oxides) or taste and/or odor corrigents.

For human use, in the case of oral administration, it is recommendable to administer doses of from 0.001 to 50 mg/kg, preferably of 0.01 mg/kg to 20 mg/kg. In the case of parenteral administration, such as, for example, intravenously or via mucous membranes nasally, buccally or inhalationally, it is recommendable to use doses of 0.001 mg/kg to 0.5 mg/kg.

In spite of this, it can be necessary in certain circumstances to depart from the amounts mentioned, namely as a function of body weight, application route, individual behaviour towards the active component, manner of preparation and time or interval at which application takes place. It can for instance be sufficient in some cases to use less than the aforementioned minimum amount, while in other cases the upper limit mentioned will have to be exceeded. In the case of the application of larger amounts, it can be advisable to divide them into a plurality of individual doses spread through the day.

The percentages in the tests and examples which follows are, unless otherwise stated, by weight; parts are by weight. Solvent ratios, dilution ratios and concentrations reported for liquid/liquid solutions are each based on the volume.

A. Evaluation of physiological activity

The potential of the compounds of the invention to inhibit neutrophil elastase activity may be demonstrated, for example, using the following assays:

I. *In vitro* assays of human neutrophil elastase (HNE)

Assay contents:

assay buffer: 0.1 M HEPES-NaOH buffer pH 7.4, 0.5 M NaCl, 0.1% (w/v) bovine serum albumin;

suitable concentration (see below) of HNE (18 U/mg lyophil., #20927.01, SERVA Electrophoresis GmbH, Heidelberg, Germany) in assay buffer;
suitable concentration (see below) of substrate in assay buffer;
suitable concentration of test compounds diluted with assay buffer from a 10 mM stock solution in DMSO.

Example A

***In vitro* inhibition of HNE using a fluorogenic peptide substrate (continuous read-out signal, 384 MTP assay format):**

In this protocol, the elastase substrate MeOSuc-Ala-Ala-Pro-Val-AMC (#324740, Calbiochem-Novabiochem Corporation, Merck KGaA, Darmstadt, Germany) is used. The test solution is prepared by mixing 10 µl of test compound dilution, 20 µl of HNE enzyme dilution (final concentration 8 - 0.4 µU/ml, routinely 2.1 µU/ml) and 20 µl of substrate dilution (final concentration 1 mM - 1 µM, routinely 20 µM), respectively. The solution is incubated for 0 - 2 hrs at 37°C (routinely one hour). The fluorescence of the liberated AMC due to the enzymatic reaction is measured at 37°C (TECAN spectra fluor plus plate reader). The rate of increase of the fluorescence (ex. 395 nm, em. 460 nm) is proportional to elastase activity. IC_{50} values are determined by RFU-versus-[I] plots. K_m and $K_{m(app.)}$ values are determined by Lineweaver-Burk plots and converted to K_i values by Dixon plots.

The preparation examples had IC_{50} values within the range of 5 nM - 5 µM in this assay. Representative data are given in Table 1:

Example No.	IC_{50} [nM]
1	30
3	20
4	40
7	13
12	25
13	25
14	70
15	200

Table 1

Example B

***In vitro* inhibition of HNE using a fluorogenic, unsoluble elastin substrate (discontinuous read-out signal, 96 MTP assay format):**

In this protocol, the elastase substrate elastin-fluorescein (#100620, ICN Biomedicals GmbH, Eschwege, Germany) is used. The test solution is prepared by mixing 3 µl of test compound dilution, 77 µl of HNE enzyme dilution (final concentration 0.22 U/ml - 2.2 mU/ml, routinely 21.7 µU/ml) and 80 µl substrate suspension (final concentration 2 mg/ml). The suspension is incubated for 0 - 16 hrs at 37°C (routinely four hours) under slightly shaking conditions. To stop the enzymatic reaction, 160 µl of 0.1 M acetic acid are added to the test solution (final concentration 50 mM). The polymeric elastin-fluorescein is pulled down by centrifugation (Eppendorf 5804 centrifuge, 3.000 rpm, 10 min). The supernatant is transferred into a new MTP and the fluorescence of the liberated peptide fluorescein due to the enzymatic reaction is measured (BMG Fluostar plate reader). The rate of fluorescence (ex. 490 nm, em. 520 nm) is proportional to elastase activity. IC_{50} values are determined by RFU-versus-[I] plots.

II. ***In vitro* PMN elastolysis assay**

This assay is used to determine the elastolytic potential of human polymorphonuclear cells (PMNs) and assess the proportion of degradation due to neutrophil elastase [cf. Z.W. She et al., Am. J. Respir. Cell. Mol. Biol. 9, 386-392 (1993)].

Tritiated elastin, in suspension, is coated on to a 96 well plate at 10 µg per well. Test and reference [ZD-0892 (J. Med. Chem. 40, 1876-1885, 3173-3181 (1997), WO 95/21855) and α1 protease inhibitor (α1PI)] compounds are added to the wells at the appropriate concentrations. Human PMNs are separated from peripheral venous

blood of healthy donors and resuspended in culture media. The neutrophils are added to the coated wells at concentrations ranging between 1 x 10^6 to 1 x 10^5 cells per well. Porcine pancreatic elastase (1.3 μM) is used as a positive control for the assay, and α1PI (1.2 μM) is used as the positive inhibitor of neutrophil elastase. The cellular control is PMNs without compound at each appropriate cell density. The cells plus compounds are incubated in a humidified incubator at 37°C for 4 hours. The plates are centrifuged to allow the harvest of cell supernatant only. The supernatant is transferred in 75 μl volumes to corresponding wells of a 96 well Lumaplate™ (solid scintillant containing plates). The plates are dried until no liquid is visible in the wells and read in a beta counter for 3 minutes per well.

Elastolysis of the ^{3}H-elastin results in an increase in counts in the supernatant. An inhibition of this elastolysis shows a decrease, from the cellular control, of tritium in the supernatant. α1PI gave 83.46 ± 3.97% (mean ± s.e.m.) inhibition at 1.2 μM (n = 3 different donors at 3.6 x 10^5 cells per well). IC_{50} values were obtained for the reference compound ZD-0892 of 45.50 ± 7.75 nM (mean ± s.e.m.) (n = 2 different donors at 3.6 x 10^5 cells per well).

Given that ZD-0892 is a selective inhibitor of PMN elastase along with the data from α1PI inhibition, these results indicate that the majority of elastin degradation by PMNs is due to the release of neutrophil elastase, and not to another elastolytic enzyme such as matrix metalloproteases (MMPs). The compounds of this invention were evaluated for their inhibitory activity in this HNE-dependent model of neutrophil elastolysis.

III. *In vivo* model of acute lung injury in the rat

Instillation of human neutrophil elastase (HNE) into rat lung causes acute lung damage. The extent of this injury can be assessed by measuring lung haemorrhage.

Rats are anaesthetised with Hypnorm/Hypnovel/water and instilled with HNE or saline delivered by microsprayer into the lungs. Test compounds are administered by intravenous injection, by oral gavage or by inhalation at set times prior to the administration of HNE. Sixty minutes after the administration of elastase animals are killed by an anaesthetic overdose (sodium pentobarbitone) and the lungs lavaged with 2 ml heparinised phosphate buffered saline (PBS). Bronchoalveolar lavage (BAL) volume is recorded and the samples kept on ice. Each BAL sample is centrifuged at 900 r.p.m. for 10 minutes at 4-10°C. The supernatant is discarded and the cell pellet resuspended in PBS and the sample spun down again. The supernatant is again discarded and the cell pellet resuspended in 1 ml 0.1% cetyltrimethyl-ammonium bromide (CTAB) / PBS to lyse the cells. Samples are frozen until blood content is assayed. Prior to the haemorrhage assay the samples are defrosted and mixed. 100 µl of each sample are placed into a separate well of a 96 well flat-bottomed plate. All samples are tested in duplicate. 100 µl 0.1% CTAB/PBS is included as a blank. The absorbance of the well contents is measured at 415 nm using a spectrophotometer. A standard curve is constructed by measuring the OD at 415 nm of different concentrations of blood in 0.1% CTAB/PBS. Blood content values are calculated by comparison to the standard curve (included in each plate) and normalised for the volume of BAL fluid retrieved.

The compounds of this invention were evaluated intravenously, orally or by inhalation for their inhibitory activity in this model of HNE-induced haemorrhage in the rat.

B. Examples

Abbreviations:

DCI	direct chemical ionisation (for MS)
DMSO	dimethylsulfoxide
EI	electron impact ionisation (for MS)
ESI	electro-spray ionisation (for MS)
HPLC	high pressure liquid chromatography
LC-MS	liquid chromatography coupled with mass spectroscopy
Mp.	melting point
MS	mass spectroscopy
NMR	nuclear magnetic resonance
of th.	of theoretical (yield)
R_t	retention time (for HPLC)

General methods:

All reactions were carried out under an argon atmosphere unless otherwise noted. Solvents were used as purchased from Aldrich without further purification. "Silica gel" or "Silica" refers to Silica gel 60 (0.040 mm-0.063 mm) from Merck KGaA company. Compounds purified over preparative HPLC were purified over a RP18-column with acetonitrile and water as the eluent, using a 1:9 to 9:1 gradient.

LC-MS and HPLC methods:

Method 1 (LC-MS)

Instrument MS: Micromass ZQ; Instrument HPLC: Waters Alliance 2790; Column: Symmetry C 18, 50 mm x 2.1 mm, 3.5 µm; Eluent A: water + 0.05% formic acid;

Eluent B: acetonitrile + 0.05% formic acid; Gradient: 0.0 min 10% B → 3.5 min 90% B → 5.5 min 90% B; Oven: 50°C; Flow: 0.8 ml/min; UV-detection: 210 nm

Method 2 (LC-MS)

Instrument: Micromass Quattro LCZ, HP1100; Column: Symmetry C18, 50 mm x 2.1 mm, 3.5 µm; Eluent A: water + 0.05% formic acid; Eluent B: acetonitrile + 0.05% formic acid; Gradient: 0.0 min 90% A → 4.0 min 10% A → 6.0 min 10% A; Oven: 40°C; Flow: 0.5 ml/min; UV-detection: 208-400 nm

Method 3 (LC-MS)

Instrument: Micromass Platform LCZ, HP1100; Column: Symmetry C18, 50 mm x 2.1 mm, 3.5 µm; Eluent A: water + 0.05% formic acid; Eluent B: acetonitrile + 0.05% formic acid; Gradient: 0.0 min 90% A → 4.0 min 10% A → 6.0 min 10% A; Oven: 40°C; Flow: 0.5 ml/min; UV-detection: 208-400 nm

Method 4 (LC-MS)

Instrument: Waters Alliance 2790 LC; Column: Symmetry C18, 50 mm x 2.1 mm, 3.5 µm; Eluent A: water + 0.1% formic acid; Eluent B: acetonitrile + 0.1% formic acid; Gradient: 0.0 min 5% B → 5.0 min 10% B → 6.0 min 10% B; Temperature: 50°C; Flow: 1.0 ml/min; UV-detection: 210 nm

Method 5 (HPLC)

Instrument: HP 1100 with DAD-detection; Column: Kromasil RP-18, 60 mm x 2 mm, 3.5 µm; Eluent A: 5 ml $HClO_4$/l H_2O; Eluent B: acetonitrile; Gradient: 0 min 2% B, 0.5 min 2% B, 4.5 min 90% B, 6.5 min 90% B; Temperature: 30°C; Flow: 0.75 ml/min; UV-detection: 210 nm

Method 6 (LC-MS)

Instrument MS: Micromass ZQ; Instrument HPLC: Waters Alliance 2790; Column: UPTISPHERE HDO, 50 mm x 2.0 mm, 3.0 µm; Eluent A: water + 0.05% formic acid; Eluent B: acetonitrile + 0.05% formic acid; Gradient: 0.0 min 5% B → 2.0 min

40% B → 4.5 min 90% B → 5.5 min 90% B; Oven: 45°C; Flow: 0.75 ml/min; UV-detection: 210 nm

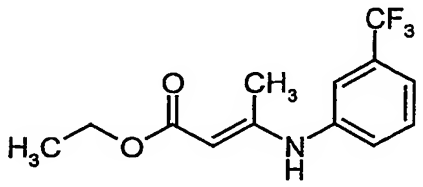
Method 7 (LC-MS)

Instrument: Micromass Platform LCZ, HP1100; Column: Grom-SIL120 ODS-4 HE, 50 mm x 2.0 mm, 3 µm; Eluent A: water + 0.05% formic acid; Eluent B: acetonitrile + 0.05% formic acid; Gradient: 0.0 min 100% A → 0.2 min 100% A → 2.9 min 30% A → 3.1 min 10% A → 4.5 min 10% A; Oven: 55°C; Flow: 0.8 ml/min; UV-detektion: 208-400 nm.

Starting Materials:

Example 1A

Ethyl-3-{[3-(trifluoromethyl)phenyl]amino}-2-butenoate



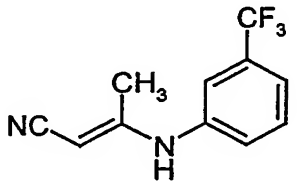
3-Trifluoromethylaniline (2.50 g, 15.5 mmol) and ethyl acetoacetate (2.32 g, 17.8 mmol) are dissolved in absolute ethanol in a 500 ml round bottom flask equipped with a stir bar and a reflux condenser. Magnesium sulphate monohydrate (2.58 g, 18.6 mmol) and glacial acetic acid (14 mg, 0.23 mmol) are added. The suspension is stirred rigorously at reflux for 16 hours under an argon atmosphere. The crude reaction mixture is cooled to room temperature, filtered and concentrated *in vacuo* to give an oil. The oil is chromatographed over silica gel with cyclohexane/ethyl acetate mixtures as eluent to yield a pale yellow oil which is analytically pure.

Yield: 1 g (27% of th.)

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.2 (t, 3H); 2.0 (s, 3H); 4.1 (q, 2H); 4.8 (s, 1H); 7.5 (m, 4H); 10.4 (s, 1H) ppm.

Example 2A

3-{[3-(Trifluoromethyl)phenyl]amino}-2-butenenitrile



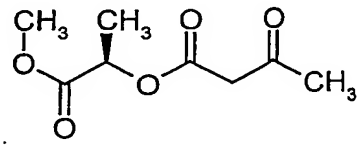
3-Aminocrotonitrile (1.0 g, 12.2 mmol), 3-trifluoromethylaniline (2.0 g, 12.4 mmol), and acetic acid (1.23 g, 20.5 mmol) are dissolved in water (8 ml). The reaction mixture is stirred at room temperature for 30 minutes. The mixture is extracted with toluene three times and the organic phase is dried over sodium sulfate. The solvent is removed *in vacuo* and the residue is purified by column chromatography on silica with cyclohexane/ethyl acetate mixtures as eluent.

Yield: 0.64 g (23% of th.)

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.2 (s, 3H); 4.6 (s, 1H); 7.4-7.6 (m, 4H); 9.0 (s, 1H) ppm.

Example 3A

(1R)-2-Methoxy-1-methyl-2-oxoethyl 3-oxobutanoate



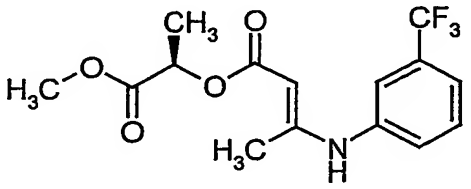
Methyl (2R)-2-hydroxypropanoate (5.0 g, 48 mmol) and triethylamine (49 mg, 0.48 mmol) are dissolved in toluene (40 ml). At 90°C, diketene (5.2 g, 62.4 mmol) is added dropwise. The reaction mixture is stirred at 100°C for one hour. After cooling to room temperature, the mixture is poured into ice-water. The phases are separated and the aqueous phase is extracted with toluene two times. The combined organic phases are dried over sodium sulfate, the solvent is removed *in vacuo* and the residue is purified by column chromatography on silica with cyclohexane/ethyl acetate mixtures as eluent.

Yield: 8 g (89% of th.)

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.4 (d, 3H); 2.2 (s, 3H); 3.7 (s, 3H, s, 2H); 5.1 (q, 1H) ppm.

Example 4A

(1R)-2-Methoxy-1-methyl-2-oxoethyl (2E)-3-{[3-(trifluoromethyl)phenyl]amino}-2-butenoate



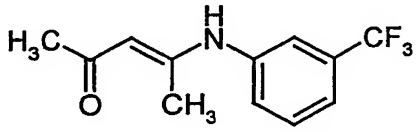
Example 3A (1 g, 5.31 mmol) and 3-trifluoromethylaniline (0.98 g, 6.11mmol) are dissolved in ethanol (20 ml), and acetic acid (6 mg, 0.11 mmol) and magnesium sulfate monohydrate (1.28 g, 10.63 mmol) are added. The reaction mixture is stirred at reflux overnight. The mixture is filtrated, the solution is evaporated to dryness *in vacuo* and the residue is purified by column chromatography on silica with cyclohexane/ethyl acetate mixtures as eluent.

Yield: 0.8 g (45% of th.)

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.3 (d, 3H); 2.3 (s, 3H); 3.6 (s, 3H); 4.8 (s, 1H); 5.0 (m, 1H); 7.5 (m, 4H); 8.9 (s, 1H) ppm.

Example 5A

4-{[3-(Trifluoromethyl)phenyl]amino}-3-penten-2-one



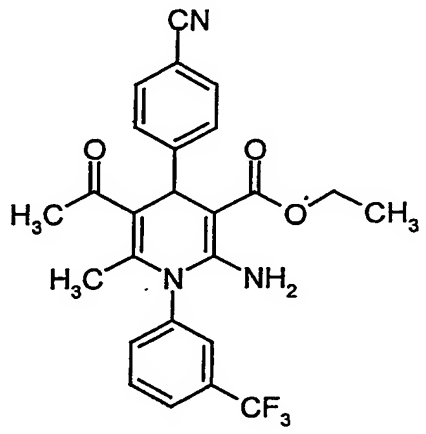
Acetylacetone (15.53 g, 155 mmol), 3-trifluoromethylaniline (5.00 g, 31 mmol), and 4-toluenesulfonic acid (0.53 g, 3.1 mmol) are dissolved in toluene (50 ml). The reaction mixture is refluxed overnight with a Dean-Stark trap to remove water. After cooling to room temperature, the solvent is removed *in vacuo* and the residue is purified by column chromatography on silica with cyclohexane/ethyl acetate mixtures as eluent.

Yield: 5.46 g (72% of th.)

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 2.0 (s, 3H); 2.1 (s, 3H); 5.3 (s, 1H); 7.5 (m, 4H); 12.5 (s, 1H) ppm.

Example 6A

Ethyl 5-acetyl-2-amino-4-(4-cyanophenyl)-6-methyl-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-3-pyridinecarboxylate



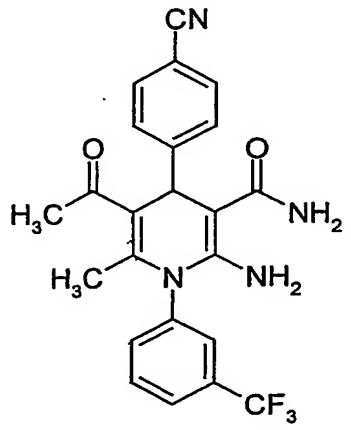
Example 5A (100 mg, 0.41 mmol) is dissolved in ethanol (2 ml), and 4-cyanobenzaldehyde (54 mg, 0.41 mmol), ethyl cyanoacetate (47 mg, 0.41 mmol) and piperidine (70 mg, 0.82 mmol) are added. The reaction mixture is stirred at reflux overnight. After cooling to room temperature, the solvent is removed *in vacuo* and the residue is purified by column chromatography on silica with dichloromethane as the eluent.

Yield: 26 mg (14% of th.)

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.2 (t, 3H); 1.8 (s, 3H); 2.2 (s, 3H); 4.0 (m, 2H); 5.0 (s, 1H); 6.7 (br.s, 2H); 7.5 (m, 2H); 7.7 (m, 1H); 7.8 (m, 4H); 7.9 (m, 1H) ppm.

Example 7A

5-Acetyl-2-amino-4-(4-cyanophenyl)-6-methyl-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-3-pyridinecarboxamide



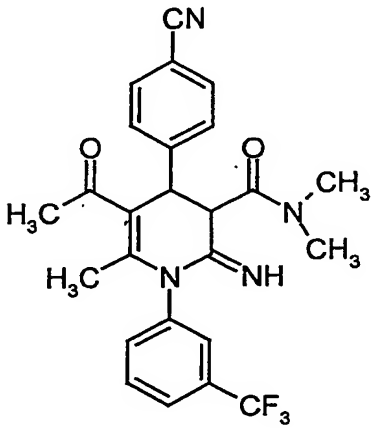
Example 5A (750 mg, 3.08 mmol) is dissolved in ethanol (5 ml), and 4-cyano-benzaldehyde (404 mg, 3.08 mmol), cyanoacetamide (260 mg, 3.08 mmol) and piperidine (26 mg, 0.31 mmol) are added. The reaction mixture is stirred at reflux overnight. After cooling to room temperature, the solvent is removed *in vacuo* and the residue is purified by column chromatography on silica with dichloromethane as the eluent.

Yield: 160 mg (12% of th.)

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.8 (s, 3H); 2.2 (s, 3H); 4.9 (s, 1H); 6.7 (br.s, 2H); 6.9 (br.s, 2H); 7.5 (m, 3H); 7.8 (m, 2H); 7.9 (m, 1H); 8.0 (m, 2H) ppm.

Example 8A

5-Acetyl-4-(4-cyanophenyl)-2-imino-N,N,6-trimethyl-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-3-pyridinecarboxamide



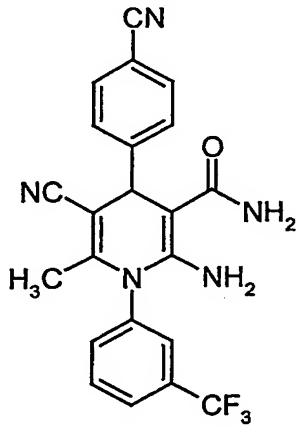
Example 5A (750 mg, 3.08 mmol) is dissolved in ethanol (5 ml), and 4-cyano-benzaldehyde (404 mg, 3.08 mmol), 2-cyano-N,N-dimethylacetamide (260 mg, 3.08 mmol) and piperidine (26 mg, 0.31 mmol) are added. The reaction mixture is stirred at reflux overnight. After cooling down to room temperature, the solvent is removed *in vacuo* and the residue is purified by column chromatography on silica with dichloromethane as the eluent.

Yield: 88 mg (6% of th.)

^{1}H-NMR (300 MHz, DMSO-d_6): δ =2.0 (s, 3H); 2.1 (s, 3H); 2.5 (s, 3H); 2.9 (s, 3H); 4.1 (d, 1H); 4.5 (d, 1H); 7.6 (m, 3H); 7.7 (m, 1H); 7.8 (m, 3H); 8.2 (s, 1H) ppm.

Example 9A

2-Amino-5-cyano-4-(4-cyanophenyl)-6-methyl-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-3-pyridinecarboxamide



Example 2A (100 mg, 0.44 mmol), 4-formylbenzonitrile (57.97 mg, 0.44 mmol) and 2-cyanoacetamide (37.17 mg, 0.44 mmol) are dissolved in ethanol (2 ml) under an argon atmosphere. Piperidine (3.76 mg, 0.04 mmol) is added, and the mixture is stirred at reflux overnight. The product is precipitated from the reaction mixture at 4°C. The precipitate is filtered, washed twice with ethanol and dried. The solid is purified by column chromatography with dichloromethane/methanol 100:1 as eluent.

Yield: 63 mg (34% of th.)

LC-MS (method 3): $R_t = 4.21$ min

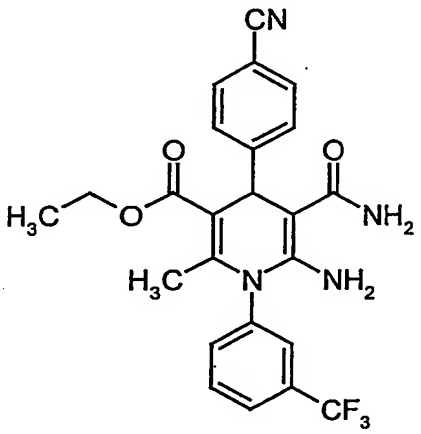
MS (EI): m/z = 424 $[M+H]^+$

HPLC (method 5): $R_t = 3.99$ min

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.68 (s, 3H); 4.76 (s, 1H); 6.42 (br.s, 2H); 7.24 (br.s, 2H); 7.63 (d, 2H); 7.77 (d, 2H); 7.82-7.95 (m, 4H) ppm.

Example 10A

Ethyl 6-amino-5-(aminocarbonyl)-4-(4-cyanophenyl)-2-methyl-1-[3-(trifluoromethyl)-phenyl]-1,4-dihydro-3-pyridinecarboxylate



Example 1A (100 mg, 0.37 mmol), 4-formylbenzonitrile (48.00 mg, 0.37 mmol) and 2-cyanoacetamide (30.77 mg, 0.37 mmol) are dissolved in ethanol (2 ml). Piperidine (1.56 mg, 0.02 mmol) is added, and the mixture is stirred at reflux. After one hour, piperidine (9.35 mg, 0.11 mmol) is again added, and the reaction is stirred overnight at reflux. After the reaction is finished, the mixture is purified by flash chromatography over silica gel with dichloromethane and dichloromethane/methanol 100:1 → 80:1 as eluent.

Yield: 40 mg (23% of th.)

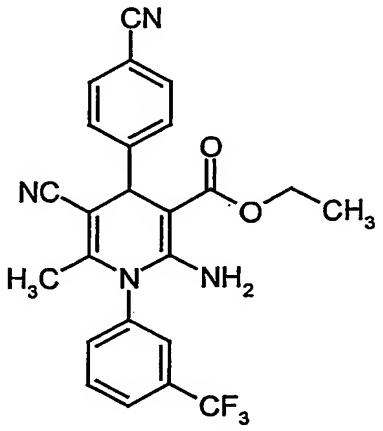
HPLC (method 5): R_t= 4.18 min

MS (EI): m/z = 471 $[M+H]^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.19 (t, 3H); 1.87 (s, 3H); 4.06 (q, 2H); 4.90 (s, 1H); 6.45 (br.s, 2H); 7.03 (br.s, 2H); 7.61 (d, 2H); 7.68 (d, 2H); 7.72-7.79 (m, 3H); 7.89 (d, 1H) ppm.

Example 11A

Ethyl 2-amino-5-cyano-4-(4-cyanophenyl)-6-methyl-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-3-pyridinecarboxylate



Example 2A (100 mg, 0.44 mmol), 4-formylbenzonitrile (57.97 mg, 0.44 mmol) and ethyl cyanoacetate (50.01 mg, 0.44 mmol) are dissolved in ethanol (2 ml) under an argon atmosphere. Piperidine (3.76 mg, 0.04 mmol) is added, and the mixture is stirred at reflux overnight. After cooling to room temperature, the precipitate is filtered and washed twice with ethanol. The crude solid product is purified by column chromatography over silica gel with cyclohexane/ethyl acetate mixtures as eluent.

Yield: 63 mg (32% of th.)

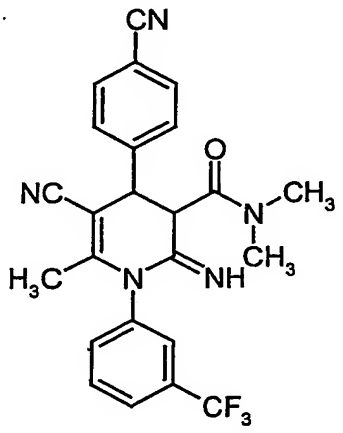
HPLC (method 5): R_t= 4.89 min

MS (EI): m/z = 453 $[M+H]^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.97 (t, 3H); 1.72 (s, 3H); 3.88 (q, 2H); 4.59 (s, 1H); 7.04 (br.s, 2H); 7.56 (d, 2H); 7.76-7.86 (m, 4H); 7.91-7.96 (m, 1H); 7.98 (s, 1H) ppm.

Example 12A

5-Cyano-4-(4-cyanophenyl)-2-imino-N,N,6-trimethyl-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-3-pyridinecarboxamide



Example 2A (100 mg, 0.44 mmol), 4-formylbenzonitrile (57.97 mg, 0.44 mmol) and 2-cyano-N,N-dimethylacetamide (49.57 mg, 0.44 mmol) are dissolved in ethanol (2 ml). Piperidine (3.76 mg, 0.04 mmol) is added, and the mixture is stirred at reflux overnight. After cooling to room temperature, the crude product is purified by column chromatography with cyclohexane/ethyl acetate 20:1; 10:1, 8:1, 6:1, 4:1, 2:1, 1:1, 1:2 and dichloromethane/methanol 100:1, 50:1, 20:1 as eluent. The product fractions are re-purified by HPLC.

Yield: 70 mg (35% of th.)

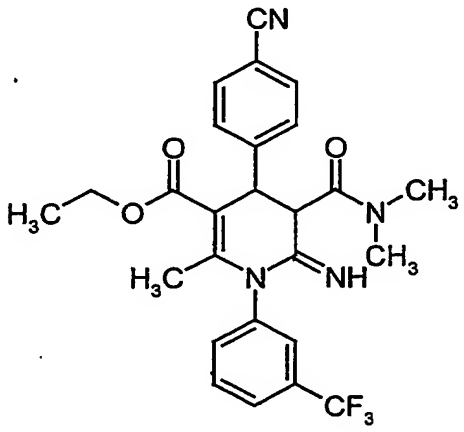
LC-MS (method 1): $R_t = 2.49$ min

MS (EI): m/z = 452 $[M+H]^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.90 (s, 3H); 2.89 (s, 3H); 3.14 (s, 3H); 4.12-4.17 (m, 1H); 4.28-4.33 (m, 1H); 7.60 (d, 2H); 7.66-7.85 (m, 4H); 7.89 (d, 2H); 8.52 (s, 1H) ppm.

Example 13A

Ethyl 4-(4-cyanophenyl)-5-[(dimethylamino)carbonyl]-6-imino-2-methyl-1-[3-(trifluoromethyl)phenyl]-1,4,5,6-tetrahydro-3-pyridinecarboxylate



Example 1A (200 mg, 0.73 mmol), 4-formylbenzonitrile (95.98 mg, 0.73 mmol) and 2-cyano-N,N-dimethylacetamide (82.07 mg, 0.73 mmol) are dissolved in ethanol (4 ml). Piperidine (6.23 mg, 0.07 mmol) are added, and the mixture is stirred at reflux overnight. After cooling down to room temperature, the crude product is purified by column chromatography on silica with cyclohexane/ethyl acetate 2:1 and dichloromethane/methanol 100:1, 40:1 as eluent.

Yield: 29 mg (8% of th.)

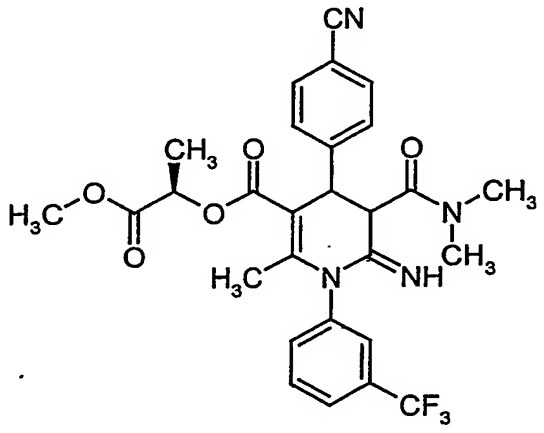
LC-MS (method 2): R_t = 3.31 min

MS (EI): m/z = 498 $[M]^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.04 (t, 3H); 2.08 (s, 3H); 2.89 (s, 3H); 3.21 (s, 3H); 3.97 (q, 2H); 4.20 (s, 1H); 4.35 (s, 1H); 7.54 (d, 2H); 7.59-7.65 (m, 2H); 7.67-7.76 (m, 2H); 7.83 (d, 2H); 8.27 (s, 1H) ppm.

Example 14A

3-Ethyl 5-[(1R)-2-methoxy-1-methyl-2-oxoethyl] 2-amino-4-(4-cyanophenyl)-6-methyl-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-3,5-pyridinedicarboxylate



Example 4A (100 mg, 0.30 mmol) and 4-formylbenzonitrile (39.58 mg, 0.30 mmol) are dissolved in ethanol (2 ml). To this mixture, ethyl cyanoacetate (34.14 mg, 0.30 mmol) and piperidine (2.57 mg, 0.03 mmol) are added. The reaction is stirred for 30 min at room temperature and at reflux overnight. After cooling to room temperature, a precipitate is obtained. The solid is filtered and the crude product is purified by column chromatography on silica gel with dichloromethane and dichloromethane / methanol 100:1, 40:1 as eluent.

Yield: 55 mg (34% of th.) as a mixture of diastereomers

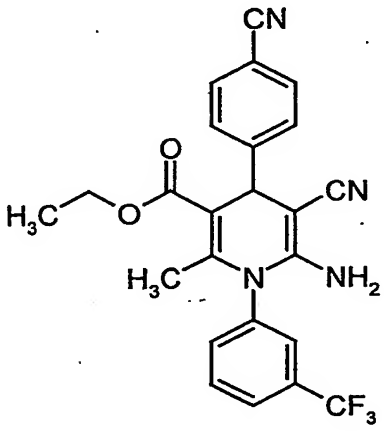
HPLC (method 5): R_t= 4.63 min

MS (EI): m/z = 558 $[M+H]^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.10 (t, 6H); 1.3 (d, 3H); 1.4 (d, 3H); 1.91 (s, 3H); 1.96 (s, 3H); 3.54 (s, 3H); 3.63 (s, 3H); 3.92-4.05 (m, 4H); 4.85-4.96 (m, 2H); 4.98 (s, 2H); 6.83 (br.s, 4H); 7.51 (m, 4H); 7.73 (m, 6H); 7.77-7.93 (m, 6H) ppm.

Example 15A

Ethyl 6-amino-5-cyano-4-(4-cyanophenyl)-2-methyl-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-3-pyridinecarboxylate



The compound is prepared as described for Example 14A with 100 mg (0.37 mmol) of the compound of Example 1A, 48 mg (0.37 mmol) 4-formylbenzonitrile, 24.18 mg (0.37 mmol) malononitrile and 3.12 mg (3.6 µl, 0.04 mmol) piperidine in 2 ml ethanol. The product is purified by HPLC.

Yield: 33 mg (20% of th.)

HPLC (method 5): R_t= 4.91 min

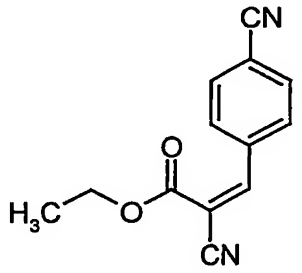
LC-MS (method 4): R_t = 3.59 min

MS (EI): m/z = 453 $[M+H]^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.04 (t, 3H); 1.94 (s, 3H); 3.96 (q, 2H); 4.60 (s, 1H); 5.53 (s, 2H); 7.50 (d, 2H); 7.66 (d, 1H); 7.72-7.91 (m, 5H) ppm.

Example 16A

Ethyl-2-cyano-3-(4-cyanophenyl)-2-propenoate



4-Cyanobenzaldehyde (3.00 g, 22.9 mmol) and ethyl cyanoacetate (2.59 g, 22.9 mmol) are dissolved in absolute ethanol (100 ml). Piperidine (0.097 g, 1.14 mmol) is added, and the solution is stirred at room temperature until no more starting material is apparent by tlc. This takes approx. 2 hours during which time a precipitate is formed. The precipitate is filtered and recrystallised, or alternatively, the crude reaction mixture is concentrated *in vacuo* and chromatographed over silica with cyclohexane/ethyl acetate mixtures as eluent to yield a white solid.

Yield: 5 g (96% of th.)

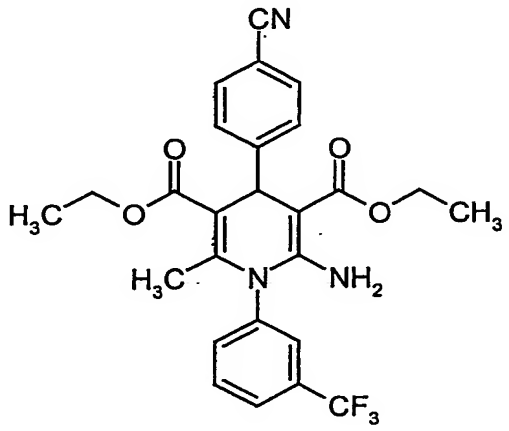
Mp.: 173-174°C

HPLC (method 5): $R_t = 4.47$ min.

^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.24$ (s, 1H); 8.05 (d, 2H); 7.78 (d, 2H); 4.41 (q, 2H); 1.41 (t, 3H) ppm.

Example 17A

Diethyl 2-amino-4-(4-cyanophenyl)-6-methyl-1-[3-(trifluoromethyl)phenyl]-1,4-dihydro-3,5-pyridinedicarboxylate



Cyanoethylacetate (2.07 g, 18.3 mmol) and 4-cyanobenzaldehyde (2.40 g, 18.3 mmol) are dissolved in ethanol (125 ml) under an argon atmosphere. Piperidine (46.7 mg, 0.55 mmol) is added, and the reaction mixture is stirred for 2 hours at room temperature. An ethanol (300 ml) solution of Example 1A (5.00 g, 18.3 mmol) and additional piperidine (0.156 g, 1.83 mmol) is added, and the reaction mixture is stirred at reflux for 16 hours. The reaction mixture is concentrated *in vacuo* and chromatographed over silica gel with cyclohexane/ethyl acetate mixtures to give a pale yellow oil.

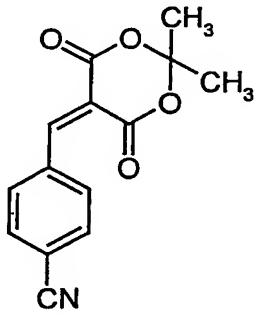
Yield: 4.55 g (42.8% of th.)

HPLC (method 5): R_t = 4.59 min

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.84-7.47 (m, 8H); 4.97 (s, 1H); 4.18 (q, 2H); 4.02 (q, 2H); 1.92 (s, 3H); 1.11 (t, 3H); 1.10 (t, 3H) ppm.

Example 18A

4-[(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl]benzonitrile



4-Cyanobenzaldehyde (5.30 g, 50.0 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (7.93 g, 55.0 mmol) are stirred in water (100 ml) at 75°C in analogy to the described procedure of Bigi *et al.* [*Tetrahedron Lett.*, **2001**, *42*, 5203-5205]. The precipitate is filtered and recrystallised from ethanol.

Yield: 3.04 g (24% of th.)

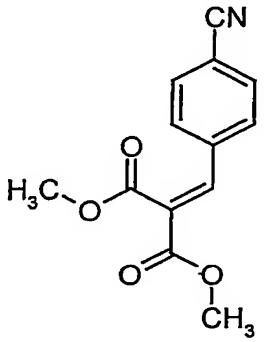
Mp.: 180°C (with decomposition)

MS (DCI, NH_3): m/z = 275 $[M+NH_4]^+$

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 8.45 (s, 1H); 8.03 (d, 2H); 7.95 (d, 2H); 1.78 (s, 6H) ppm.

Example 19A

Dimethyl 2-(4-cyanobenzylidene)malonate



Dimethyl malonate (5.04 g, 38.13 mmol), 4-cyanobenzaldehyde (5.00 g, 38.13 mmol) and piperidine (0.097 g, 1.1 mmol) are dissolved in methanol (150 ml). The reaction mixture is stirred for two days (48 hours) at room temperature. The solvent is removed *in vacuo* to afford a viscous oil which is recrystallised from methanol.

Yield: 5.3 g (57% of th.)

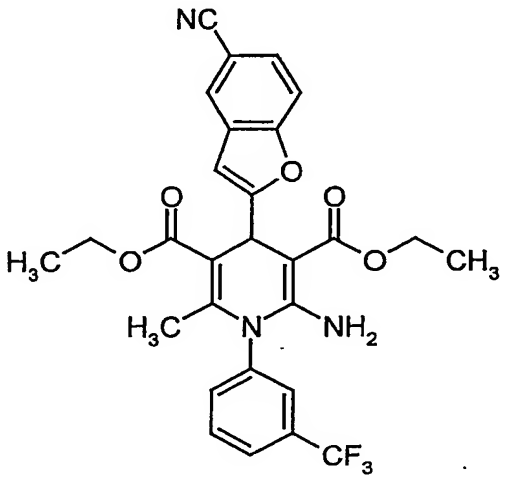
Mp.: 98-99°C

HPLC (method 5): R_t =3.94 min

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.0-7.6 (m, 5H); 3.81 (s, 3H); 3.80 (s, 3H) ppm.

Example 20A

Diethyl 2-amino-4-(5-cyano-1-benzofuran-2-yl)-6-methyl-1-[3-(trifluoromethyl)-phenyl]-1,4-dihydro-3,5-pyridinedicarboxylate



2-Formyl-1-benzofuran-5-carbonitrile (157 mg, 0.915 mmol) and ethyl cyanoacetate (103 mg, 0.915 mmol) are dissolved in ethanol (8 ml). Piperidine (2.3 mg, 0.027 mmol) is added, and the reaction mixture is stirred for two hours at room temperature. A solution of Example 1A (253 mg, 0.915 mmol) and piperidine (7.8 mg, 0.091 ml) in ethanol (2 ml) is added, and the reaction mixture is stirred at

reflux (95°C) overnight (18 h). The crude reaction mixture is concentrated *in vacuo*, dissolved in DMSO (7 ml) and purified by preparative HPLC.

Yield: 249 mg (50% of th.)

LC-MS (method 2): $R_t = 5.34$ min.

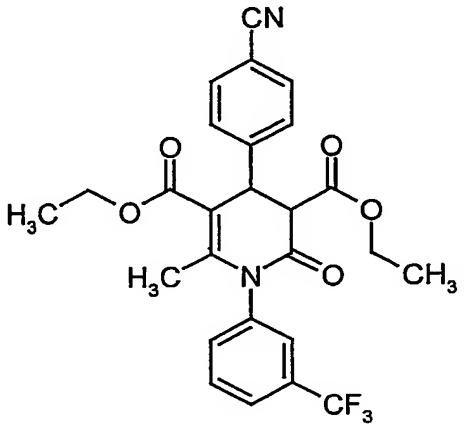
MS (EI): m/z = 540 $[M+H]^+$

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 8.11 (s, 1H); 7.99-7.64 (m, H); 6.87 (br.s, 2H); 6.63 (s, 1H); 4.25-3.92 (m, 4H); 1.98 (s, 3H); 1.31-1.09 (m, 6H) ppm.

Preparation Examples:

Example 1

Diethyl 4-(4-cyanophenyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-3,5-pyridinedicarboxylate



The compound of Example 1A (65% pure, 1.8 g, 4.3 mmol), 1,8-diazabicyclo[5.4.0]-undec-7-ene (0.065 g, 0.43 mmol) and the compound of Example 19A (1.05 g, 4.3 mmol) are dissolved in ethanol (200 ml) and stirred at reflux for 48 hours. The reaction is cooled to room temperature and the ethanol is removed *in vacuo*. The residue is chromatographed over silica gel with cyclohexane/ethyl acetate mixtures as eluent.

Yield: 0.4 g (14% of th.)

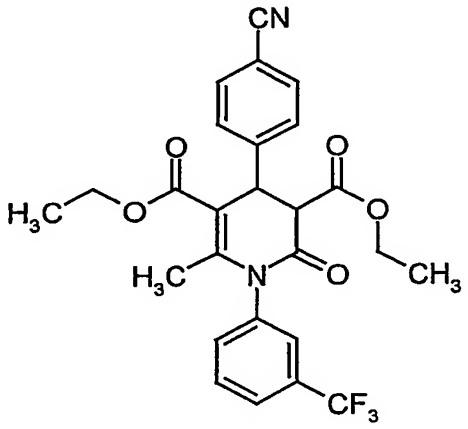
HPLC (method 5): R_t = 5.12 min.

MS (ESIneg): m/z = 499 $[M-H]^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.9-7.5 (m, 8H); 4.75 (d, 1H); 4.01 (d, 1H); 4.30-3.95 (m, 4H); 2.09 (d, 3H); 1.27-1.05 (m, 6H) ppm.

Example 2

(+)-Diethyl 4-(4-cyanophenyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-3,5-pyridinedicarboxylate



The compound of Example 1 is separated into the enantiomers via HPLC on a chiral stationary KBD 7644 silica gel column (silane-modified N-methacryloyl-D-valine-3-pentylamide fixed on silica) with an eluent mixture of *i*-hexane and ethyl acetate (1:4 v/v).

(+)-Enantiomer:

Yield: 0.4 g (14% of th.)

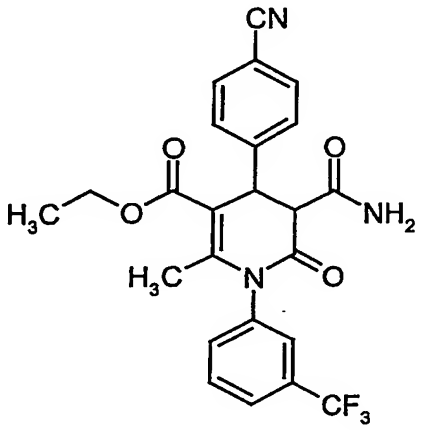
HPLC (method 5): R_t = 5.12 min

$[\alpha]^{20}_D$ = +23° (0.7 M in dichloromethane)

MS (ESIneg): m/z = 499 $[M-H]^+$

Example 3

Ethyl 5-(aminocarbonyl)-4-(4-cyanophenyl)-2-methyl-6-oxo-1-[3-trifluoromethyl)-phenyl]-1,4,5,6-tetrahydro-3-pyridinecarboxylate



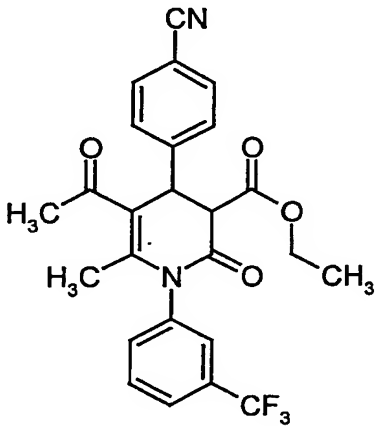
Example 10A (1 g, 2.13 mmol) is dissolved in acetic acid (20 ml) and water (1 ml). The mixture is stirred at reflux for 18 hours. After cooling to room temperature, the solvent is removed *in vacuo* and the residue is purified by column chromatography on silica with cyclohexane/ethyl acetate mixtures as eluent.

Yield: 0.27 g (27% of th.)

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.1 (t, 3H); 2.1 (s, 3H); 3.6 (d, 1H); 4.1 (q, 2H); 4.7 (d, 1H); 7.4 (m, 1H); 7.6 (m, 2H); 7.7 (m, 2H); 7.8 (m, 1H); 7.9 (m, 4H) ppm.

Example 4

Ethyl 5-acetyl-4-(4-cyanophenyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-3-pyridinecarboxylate



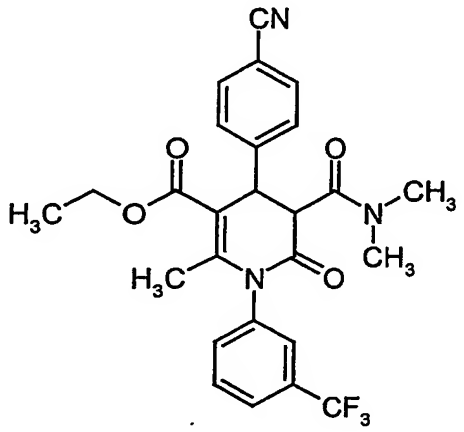
Example 6A (100 mg, 0.21 mmol) is dissolved in acetic acid (2 ml) and water (0.2 ml). The mixture is stirred at reflux for 18 hours. After cooling to room temperature, the solvent is removed *in vacuo* and the residue is purified by column chromatography on silica with cyclohexane/ethyl acetate mixtures as eluent.

Yield: 11 mg (11% of th.)

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.2 (t, 3H); 2.0 (s, 3H); 2.2 (s, 3H); 4.1 (d, 1H); 4.2 (q, 2H); 4.8 (d, 1H); 7.5 (m, 2H); 7.6 (m, 1H); 7.7 (m, 2H); 7.8 (m, 5H) ppm.

Example 5

Ethyl 4-(4-cyanophenyl)-5-[(dimethylamino)carbonyl]-2-methyl-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,4,5,6-tetrahydro-3-pyridinecarboxylate



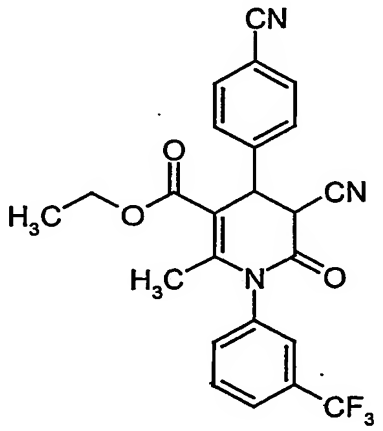
Example 13A (190 mg, 0.38 mmol) is dissolved in acetic acid (2 ml) and water (0.2 ml). The mixture is stirred at reflux for 18 hours. After cooling to room temperature, the solvent is removed *in vacuo* and the residue is purified by column chromatography on silica with cyclohexane/ethyl acetate mixtures as eluent.

Yield: 36 mg (19% of th.)

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.0 (t, 3H); 2.0 (s, 3H); 2.8 (s, 3H); 3.1 (s, 3H); 4.0 (q, 2H); 4.2 (d, 1H); 4.5 (d, 1H); 7.6 (m, 4H); 7.7 (m, 1H); 7.8 (m, 3H) ppm.

Example 6

Ethyl 5-cyano-4-(4-cyanophenyl)-2-methyl-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,4,5,6-tetrahydro-3-pyridinecarboxylate



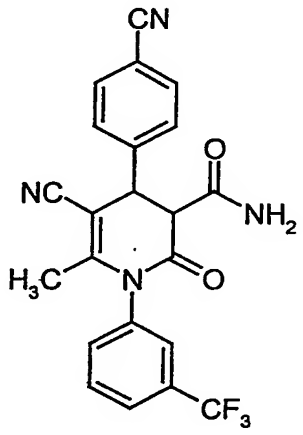
Example 15A (35 mg, 0.08 mmol) is dissolved in acetic acid (2 ml) and water (0.2 ml). The mixture is stirred at reflux for 18 hours. After cooling to room temperature, the solvent is removed *in vacuo* and the residue is purified by column chromatography on silica with dichloromethane as the eluent.

Yield: 11 mg (32% of th.)

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.1 (t, 3H); 2.1 (s, 3H); 4.1 (m, 2H); 4.7 (d, 1H); 5.2 (br. m, 1H); 7.6 (m, 2H); 7.7 (m, 2H); 7.9 (m, 4H) ppm.

Example 7

5-Cyano-4-(4-cyanophenyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-3-pyridinecarboxamide



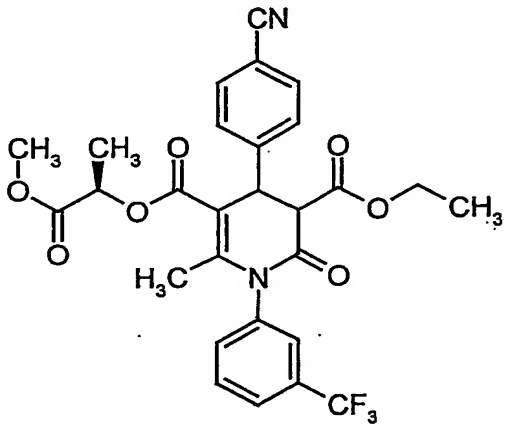
Example 9A (49 mg, 0.12 mmol) is dissolved in acetic acid (3 ml) and water (0.3 ml). The mixture is stirred at reflux for 18 hours. After cooling to room temperature, the solvent is removed *in vacuo* and the residue is purified by preparative HPLC.

Yield: 34 mg (69% of th.)

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.9 (s, 3H); 3.9 (d, 1H); 4.5 (d, 1H); 7.3 (s, 1H); 7.6 (m, 3H); 7.7 (m, 3H); 7.8 (m, 1H); 7.9 (m, 2H) ppm.

Example 8

3-Ethyl 5-[(1R)-2-methoxy-1-methyl-2-oxoethyl] 4-(4-cyanophenyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-3,5-pyridinedicarboxylate



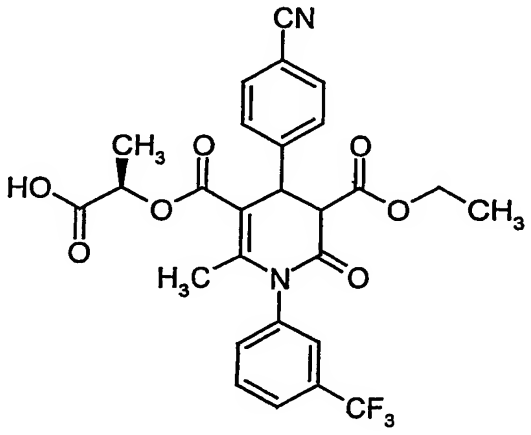
Example 14A (50 mg, 0.09 mmol) is dissolved in acetic acid (2 ml) and water (0.2 ml). The mixture is stirred at reflux for 18 hours. After cooling to room temperature, the solvent is removed *in vacuo* and the residue is purified by preparative HPLC.

Yield: 9 mg (18% of th.) as a mixture of diastereoisomers

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.2 (t, 3H, t, 3H, d, 3H); 1.4 (d, 3H); 2.1 (s, 3H, s, 3H); 3.6 (s, 3H); 3.7 (s, 3H); 4.1 (d, 1H); 4.2 (d, 1H); 4.3 (m, 4H); 4.8 (d, 1H, d, 1H); 5.0 (q, 1H); 5.1 (q, 1H); 7.5 (m, 4H); 7.6 (m, 4H); 7.8 (m, 2H); 7.9 (m, 6H) ppm.

Example 9

(2R)-2-[({4-(4-Cyanophenyl)-5-(ethoxycarbonyl)-2-methyl-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,4,5,6-tetrahydro-3-pyridinyl}carbonyl)oxy]propanoic acid



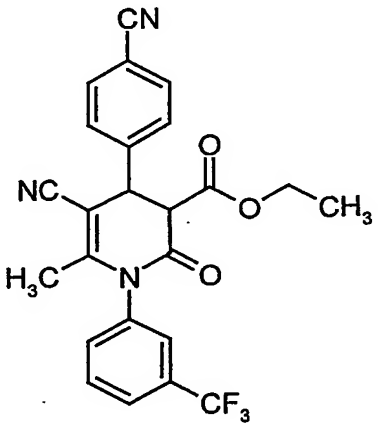
This compound is obtained as a by-product of the preparation of Example 8.

Yield: 7 mg (14% of th.) as a mixture of diastereoisomers

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.2 (t, 3H, t, 3H, d, 3H); 1.4 (d, 3H); 2.0 (s, 3H, s, 3H); 4.1 (d, 1H); 4.1 (d, 1H); 4.3 (m, 4H); 4.8 (d, 1H, d, 1H); 4.9 (q, 1H); 4.9 (q, 1H); 7.5 (m, 4H); 7.6 (m, 4H); 7.8 (m, 2H); 7.9 (m, 6H) ppm.

Example 10

Ethyl 5-cyano-4-(4-cyanophenyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-3-pyridinecarboxylate



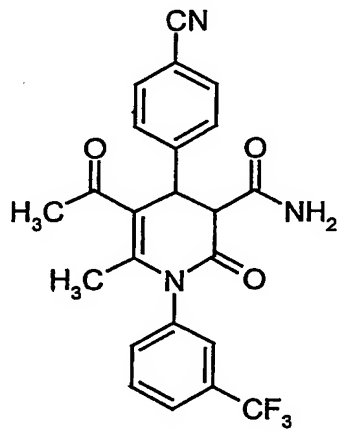
Example 11A (233 mg, 0.51 mmol) is dissolved in glacial acetic acid (5 ml) and water (1 ml). The mixture is stirred at reflux for 18 hours. After cooling to room temperature, the solvent is removed *in vacuo* and the residue is purified by column chromatography on silica with cyclohexane/ethyl acetate mixtures as eluent.

Yield: 105 mg (45% of th.)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.3 (t, 3H); 2.0 (s, 3H); 3.9 (d, 1H); 4.3 (m, 2H); 4.5 (d, 1H); 7.4 (m, 2H); 7.5 (m, 2H); 7.6 (m, 1H); 7.7 (m, 2H) ppm.

Example 11

Ethyl 5-cyano-4-(4-cyanophenyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-3-pyridinecarboxylate



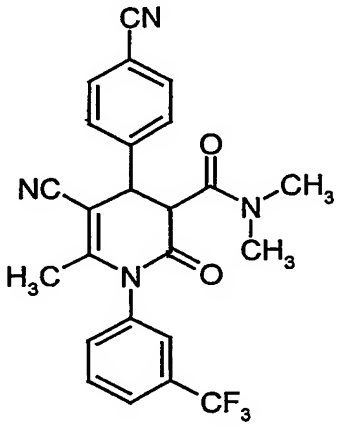
Example 7A (138 mg, 0.31 mmol) is dissolved in acetic acid (3 ml) and water (0.5 ml). The mixture is stirred at reflux for 18 hours. After cooling to room temperature, the solvent is removed *in vacuo* and the residue is purified by preparative HPLC.

Yield: 28 mg (20% of th.)

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.0 (s, 3H); 2.2 (s, 3H); 3.7 (d, 1H); 4.8 (d, 1H); 7.4 (br. s, 1H); 7.5 (m, 2H); 7.7 (m, 3H); 7.8 (m, 1H); 7.9 (m, 3H) ppm.

Example 12

5-Cyano-4-(4-cyanophenyl)-N,N,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-3-pyridinecarboxamide



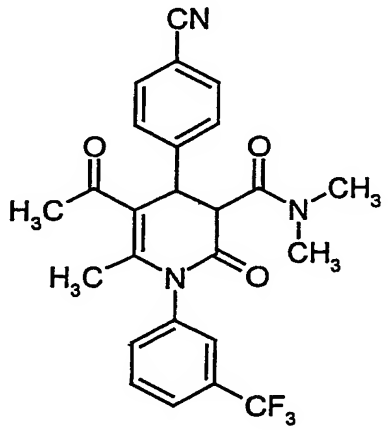
Example 12A (107 mg, 0.24 mmol) is dissolved in acetic acid (5 ml) and water (0.5 ml). The mixture is stirred at reflux for 18 hours. After cooling down to room temperature, the solvent is removed *in vacuo* and the residue is purified by preparative HPLC.

Yield: 69 mg (64% of th.)

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.9 (s, 3H); 2.7 (s, 3H), 3.0 (s, 3H); 4.6 (d/d, 1H); 4.7 (d, 1H); 7.6 (m, 2H); 7.7 (m, 1H); 7.8 (m, 2H); 7.9 (m, 3H) ppm.

Example 13

5-Acetyl-4-(4-cyanophenyl)-N,N,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-3-pyridinecarboxamide



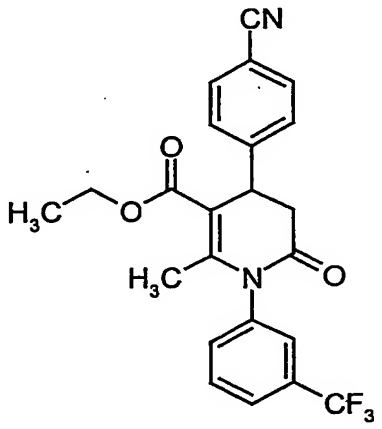
Example 8A (70 mg, 0.15 mmol) is dissolved in acetic acid (4 ml) and water (0.4 ml). The mixture is stirred at reflux for 18 hours. After cooling to room temperature, the solvent is removed *in vacuo* and the residue is purified by preparative HPLC.

Yield: 7 mg (10% of th.)

^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 2.0$ (s, 3H); 2.1 (s, 3H); 2.9 (s, 3H); 3.2 (s, 3H); 4.3 (d, 1H); 4.6 (d, 1H); 7.6 (m, 2H); 7.7 (m, 2H); 7.7 (m, 1H); 7.8 (m, 1H); 7.9 (m, 2H) ppm.

Example 14

Ethyl 4-(4-cyanophenyl)-2-methyl-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,4,5,6-tetrahydro-3-pyridinecarboxylate



4-[(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl]benzonitrile (Example 18A; 200 mg, 0.77 mmol) and ethyl (2E)-3-{[3-(trifluoromethyl)phenyl]amino}-2-butenoate (212.4 mg, 0.77 mmol) are dissolved in 1-methoxy-2-(2-methoxyethoxy)ethane (3 ml). The solution is stirred at reflux temperature overnight. The reaction mixture is cooled to room temperature and diluted with water (5 ml). After extraction with toluene (2 x 5 ml), it is dried with anhydrous sodium sulphate, filtered, and the solvent is removed *in vacuo*. The product is purified via preparative HPLC.

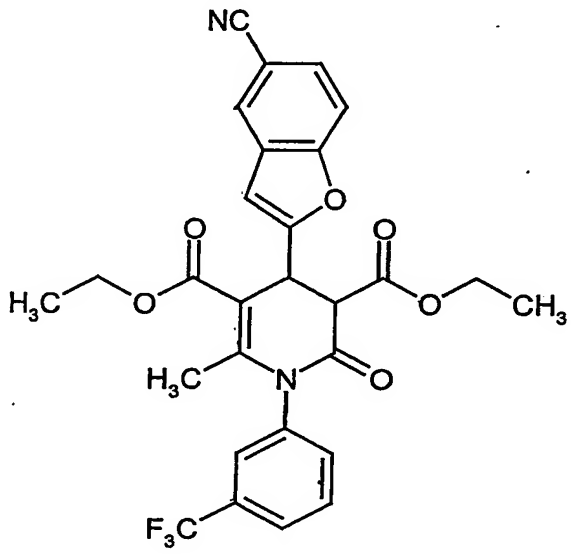
Yield: 28 mg (8% of th.)

LC-MS (method 6): $R_t = 4.05$ min

MS (ESIpos): $m/z = 429$ $[M+H]^+$.

Example 15

Diethyl 4-(5-cyano-1-benzofuran-2-yl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydro-3,5-pyridinedicarboxylate



Example 20A (110 mg, 0.204 mmol) is dissolved in acetic acid (20 ml). The mixture is stirred at reflux for 18 hours. After cooling to room temperature, the solvent is removed *in vacuo* and the residue is purified by preparative HPLC.

Yield: 10 mg (9% of th.)

LC-MS (method 7): $R_t = 4.10$ min

MS (ESIpos): $m/z = 541$ $[M+H]^+$

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 8.24-8.10 (m, 1H); 7.98-7.65 (m, 5H); 7.56-7.47 (m, 1H); 7.18-7.04 (m, 1H); 4.94 (br. d, 1H); 4.37-3.91 (m, 5H); 2.05 (s, 3H); 1.30-0.97 (m, 6H) ppm.

C. Operative examples relating to pharmaceutical compositions

The compounds according to the invention can be converted into pharmaceutical preparations as follows:

Tablet:

Composition:

100 mg of the compound of Example 1, 50 mg of lactose (monohydrate), 50 mg of maize starch (native), 10 mg of polyvinylpyrrolidone (PVP 25) (from BASF, Ludwigshafen, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg, diameter 8 mm, curvature radius 12 mm.

Preparation:

The mixture of active component, lactose and starch is granulated with a 5% solution (m/m) of the PVP in water. After drying, the granules are mixed with magnesium stearate for 5 min. This mixture is moulded using a customary tablet press (tablet format, see above). The moulding force applied is typically 15 kN.

Orally administrable suspension:

Composition:

1000 mg of the compound of Example 1, 1000 mg of ethanol (96%), 400 mg of Rhodigel (xanthan gum from FMC, Pennsylvania, USA) and 99 g of water.

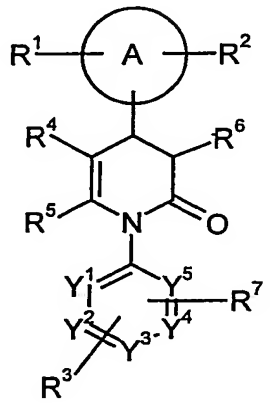
A single dose of 100 mg of the compound according to the invention is provided by 10 ml of oral suspension.

Preparation:

The Rhodigel is suspended in ethanol and the active component is added to the suspension. The water is added with stirring. Stirring is continued for about 6h until the swelling of the Rhodigel is complete.

We claim

1. Compounds of the general formula (I)



(I),

wherein

A represents an aryl or heteroaryl ring,

R^1, R^2 and R^3 independently from each other represent hydrogen, halogen, nitro, cyano, trifluoromethyl, C_1-C_6-alkyl, hydroxy, C_1-C_6-alkoxy or trifluoromethoxy, wherein C_1-C_6-alkyl and C_1-C_6-alkoxy can be further substituted with one to three identical or different radicals selected from the group consisting of hydroxy and C_1-C_4-alkoxy,

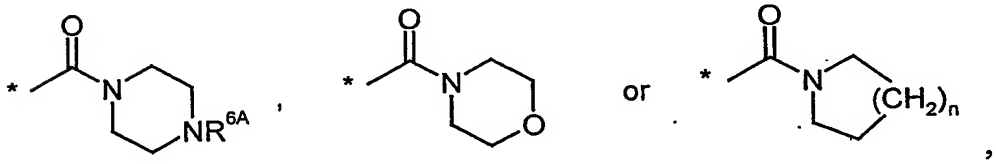
R^4 represents C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, hydroxycarbonyl, aminocarbonyl, mono- or di-C_1-C_4-alkylaminocarbonyl or cyano, wherein C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, mono- and di-C_1-C_4-alkylaminocarbonyl can be substituted with one to three identical or different radicals selected from the group consisting of hydroxy, C_1-C_4-alkoxy, hydroxycarbonyl, C_1-C_4-alkoxycarbonyl, amino, mono- and di-C_1-C_4-alkylamino, aminocarbonyl, mono- and di-C_1-C_4-alkylaminocarbonyl, C_1-C_4-alkylcarbonylamino and heteroaryl,

R^5 represents C_1-C_4-alkyl,

R^6 represents hydrogen, cyano, aminocarbonyl, mono- or di-C_1-C_4-alkyl-aminocarbonyl, C_3-C_8-cycloalkylaminocarbonyl, C_1-C_6-alkylcarbonyl, hydroxycarbonyl or C_1-C_6-alkoxycarbonyl, wherein mono- and di-C_1-C_4-alkylaminocarbonyl, C_1-C_6-alkylcarbonyl and C_1-C_6-alkoxy-carbonyl can be substituted with one to three identical or different radicals selected from the group consisting of hydroxy, C_1-C_4-alkoxy, hydroxycarbonyl, C_1-C_4-alkoxycarbonyl, amino, mono- and di-C_1-C_4-alkylamino, aminocarbonyl, mono- and di-C_1-C_4-alkylaminocarbonyl, C_1-C_4-alkylcarbonylamino, phenyl and heteroaryl,

or

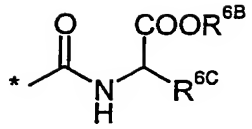
R^6 represents a moiety of the formula



wherein R^{6A} is selected from the group consisting of hydrogen and C_1-C_6-alkyl, and n represents an integer of 1 or 2,

or

R^6 represents a moiety of the formula



wherein R^{6B} is selected from the group consisting of hydrogen and C_1-C_6-alkyl, and R^{6C} is an amino acid side chain,

R^7 represents hydrogen, halogen, nitro, cyano, trifluoromethyl, C_1-C_6-alkyl, hydroxy, C_1-C_6-alkoxy or trifluoromethoxy, wherein C_1-C_6-alkyl and C_1-C_6-alkoxy can be further substituted with one to three identical or different radicals selected from the group consisting of hydroxy and C_1-C_4-alkoxy,

and

Y^1, Y^2, Y^3, Y^4 and Y^5 independently from each other represent CH or N, wherein the ring contains either 0, 1 or 2 nitrogen atoms,

and their salts, hydrates and/or solvates and their tautomeric forms.

2. Compounds of general formula (I) according to Claim 1, wherein

A represents an aryl ring,

R^1, R^2 and R^3 independently from each other represent hydrogen, fluoro, chloro, bromo, nitro, cyano, methyl, ethyl, trifluoromethyl or trifluoromethoxy,

R^4 represents C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl or cyano, wherein C_1-C_6-alkylcarbonyl and C_1-C_6-alkoxycarbonyl can be substituted with one to two identical or different radicals selected from

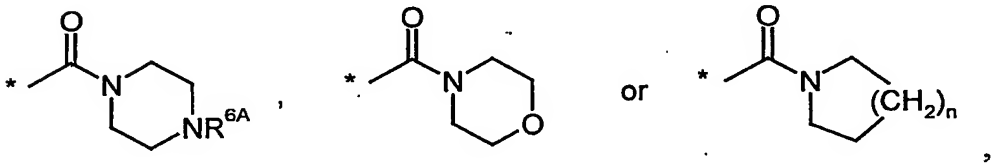
the group consisting of hydroxy, methoxy, hydroxycarbonyl, methoxycarbonyl, amino, mono- and di-C_1-C_4-alkylamino,

R^5 represents methyl or ethyl,

R^6 represents hydrogen, cyano, aminocarbonyl, mono- or di-C_1-C_4-alkylaminocarbonyl, hydroxycarbonyl or C_1-C_6-alkoxycarbonyl,

or

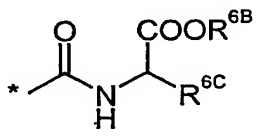
R^6 represents a moiety of the formula



wherein R^{6A} is selected from the group consisting of hydrogen, methyl and ethyl, and n represents an integer of 1 or 2,

or

R^6 represents a moiety of the formula



wherein R^{6B} is selected from the group consisting of hydrogen, methyl and ethyl, and R^{6C} is an amino acid side chain,

R^7 represents hydrogen, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, methyl or ethyl,

and

Y^1, Y^2, Y^3, Y^4 and Y^5 each represent CH.

3. Compounds of general formula (I) according to Claim 1 or 2, wherein

A represents a phenyl ring,

R^1 represents hydrogen or methyl,

R^2 represents cyano, bromo or nitro,

R^3 represents hydrogen,

R^4 represents C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxycarbonyl or cyano, wherein C_1-C_4-alkylcarbonyl and C_1-C_4-alkoxycarbonyl can be substituted with hydroxycarbonyl or C_1-C_4-alkoxycarbonyl,

R^5 represents methyl,

R^6 represents hydrogen, cyano, aminocarbonyl, mono- or di-C_1-C_4-alkylaminocarbonyl, hydroxycarbonyl or C_1-C_6-alkoxycarbonyl,

R^7 represents trifluoromethyl or nitro,

and

Y^1, Y^2, Y^3, Y^4 and Y^5 each represent CH.

4. Compounds of general formula (I) according to at least one of Claims 1 to 3, wherein A is phenyl.

5. Compounds of general formula (I) according to at least one of Claims 1 to 4, wherein R^1 is hydrogen.

6. Compounds of general formula (I) according to at least one of Claims 1 to 5, wherein R^2 is cyano.

7. Compounds of general formula (I) according to at least one of Claims 1 to 6, wherein R^3 is hydrogen.

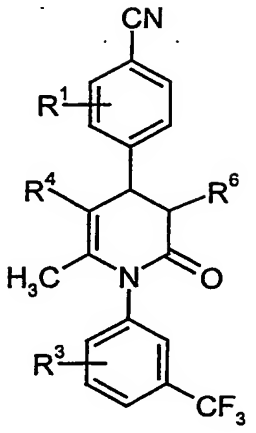
8. Compounds of general formula (I) according to at least one of Claims 1 to 7, wherein R^4 is C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl or cyano.

9. Compounds of general formula (I) according to at least one of Claims 1 to 8, wherein R^5 is methyl.

10. Compounds of general formula (I) according to at least one of Claims 1 to 9, wherein R^6 is hydrogen, cyano, aminocarbonyl, mono- and di-methyl- or -ethylaminocarbonyl, methoxycarbonyl or ethoxycarbonyl.

11. Compounds of general formula (I) according to at least one of Claims 1 to 10, wherein R^7 is trifluoromethyl or nitro.

12. Compounds of general formula (IA)

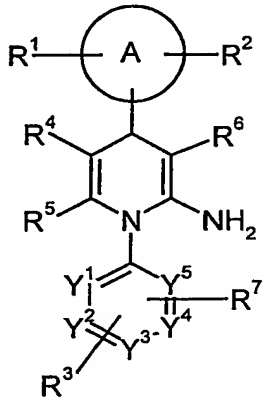


(IA),

wherein R^1, R^3, R^4 and R^6 have the meaning indicated in Claims 1 to 11.

13. Processes for synthesizing the compounds of general formula (I) or (IA), respectively, as defined in Claims 1 to 12, characterized in that

[A] compounds of the general formula (II)



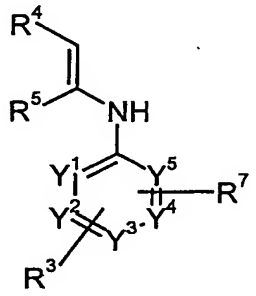
(II),

wherein R^1 to R^7, A and Y^1 to Y^5 have the meaning indicated in Claims 1 to 12,

are hydrolyzed with water,

or

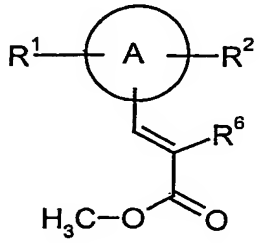
[B] compounds of the general formula (III)



(III),

wherein R^3, R^4, R^5, R^7, and Y^1 to Y^5 have the meaning indicated in Claims 1 to 12,

are reacted with compounds of the general formula (IX)

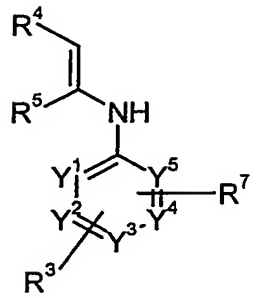


(IX),

wherein R^1, R^2, R^6 and A have the meaning indicated in Claims 1 to 12,

or

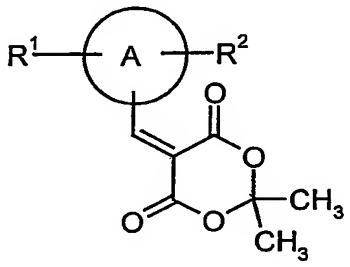
[C] compounds of the general formula (III)



(III),

wherein R^3, R^4, R^5, R^7, and Y^1 to Y^5 have the meaning indicated in Claims 1 to 12,

are reacted with compounds of the general formula (VIII)



(VIII),

wherein R^1 and R^2 have the meaning indicated in Claims 1 to 12.

14. The composition containing at least one compound of general formula (I) or (IA), as defined in Claims 1 to 12, and a pharmacologically acceptable diluent.

15. A composition according to claim 14 for the treatment of acute and chronic inflammatory processes.

16. The process for the preparation of compositions according to claim 14 and 15 characterized in that the compounds of general formula (I) or (IA), as defined in Claims 1 to 12, together with customary auxiliaries are brought into a suitable application form.

17. Use of the compounds of general formula (I) or (IA), as defined in Claims 1 to 12, for the preparation of medicaments.

18. Use according to claim 17 for the preparation of medicaments for the treatment of acute and chronic inflammatory processes.

19. Use according to claim 18, wherein the process is chronic obstructive pulmonary disease.

20. Process for controlling chronic obstructive pulmonary disease in humans and animals by administration of an neutrophil elastase inhibitory amount of at least one compound according to any of Claims 1 to 12.

Dihydropyridinone derivatives

Abstract

The invention relates to novel dihydropyridinone derivatives, processes for their preparation, and their use in medicaments, especially for the treatment of chronic obstructive pulmonary diseases.